

C O N T E N T S

The American Journal of Medicine

VOL. VI MARCH, 1949 No. 3

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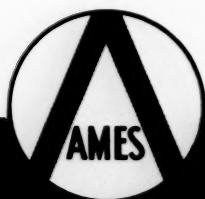
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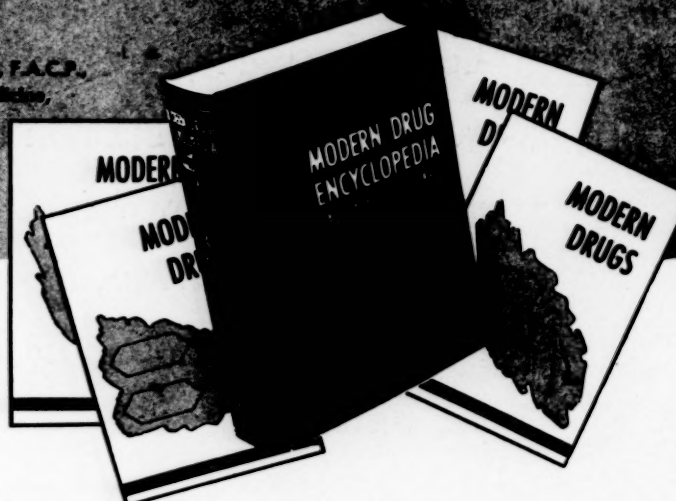
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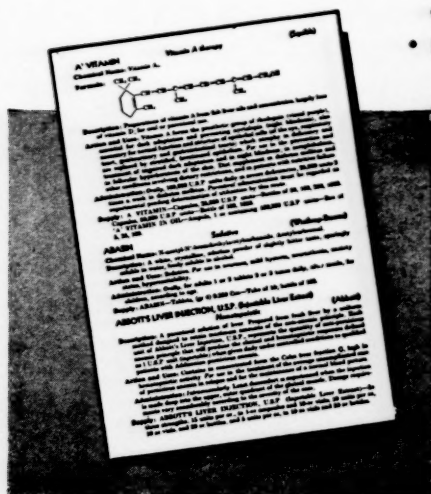
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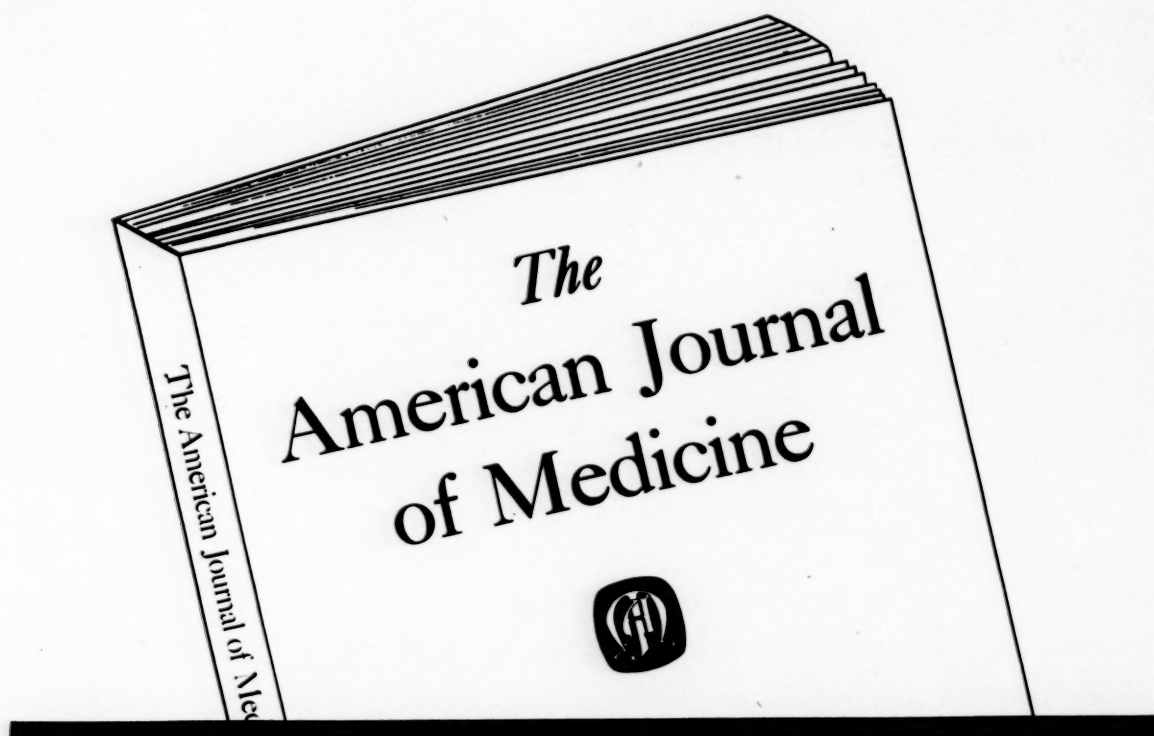
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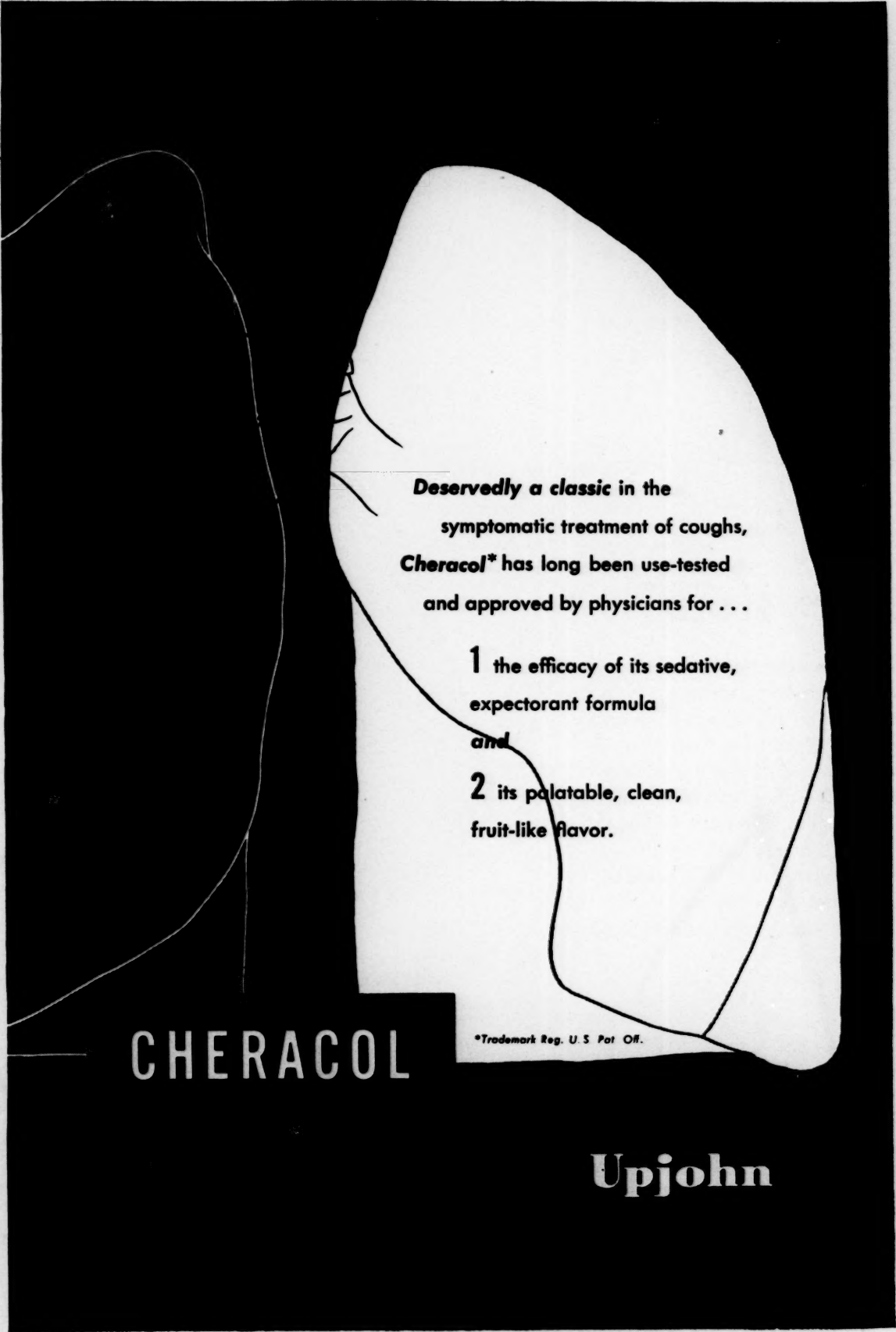
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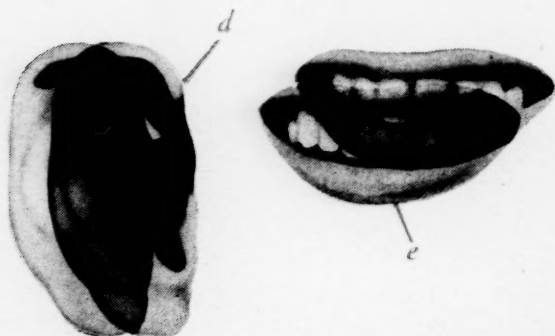
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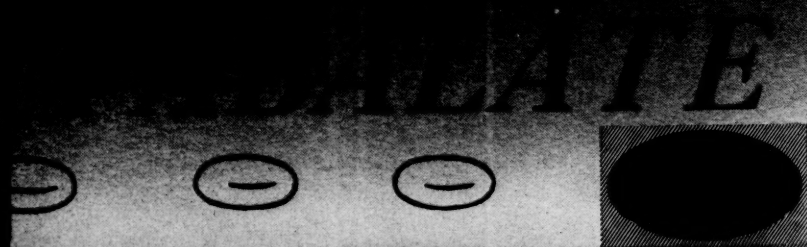
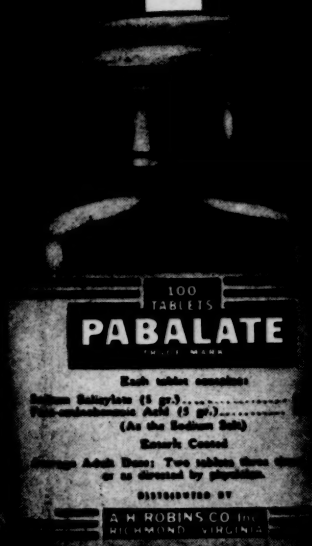


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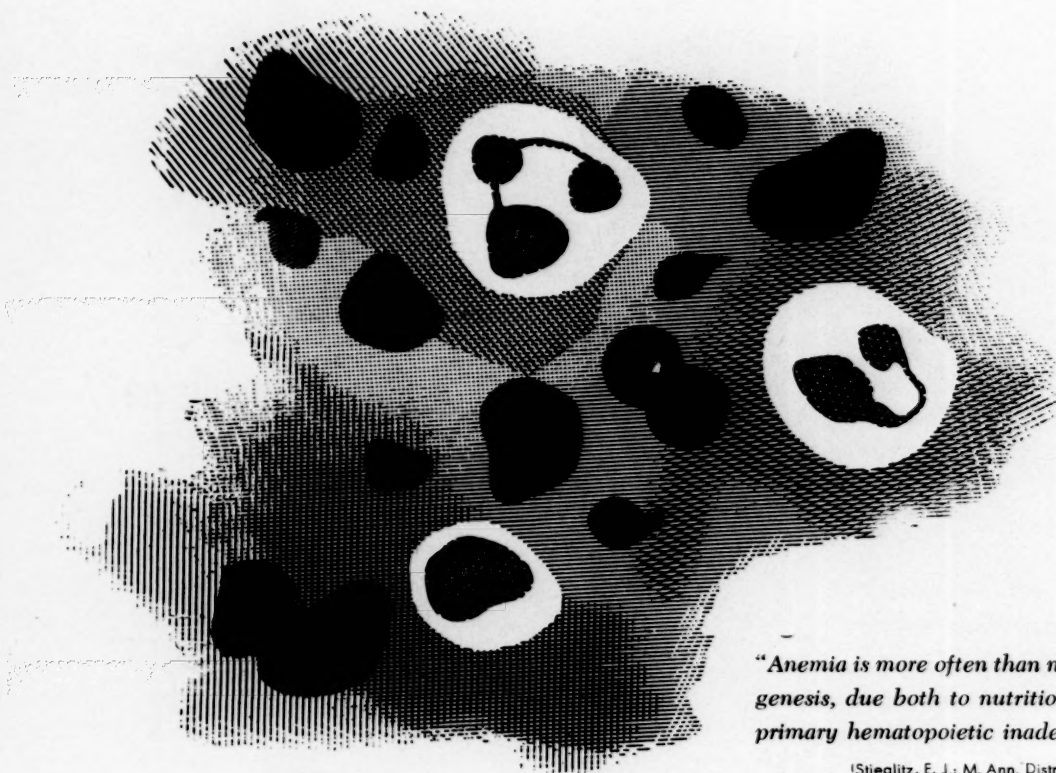
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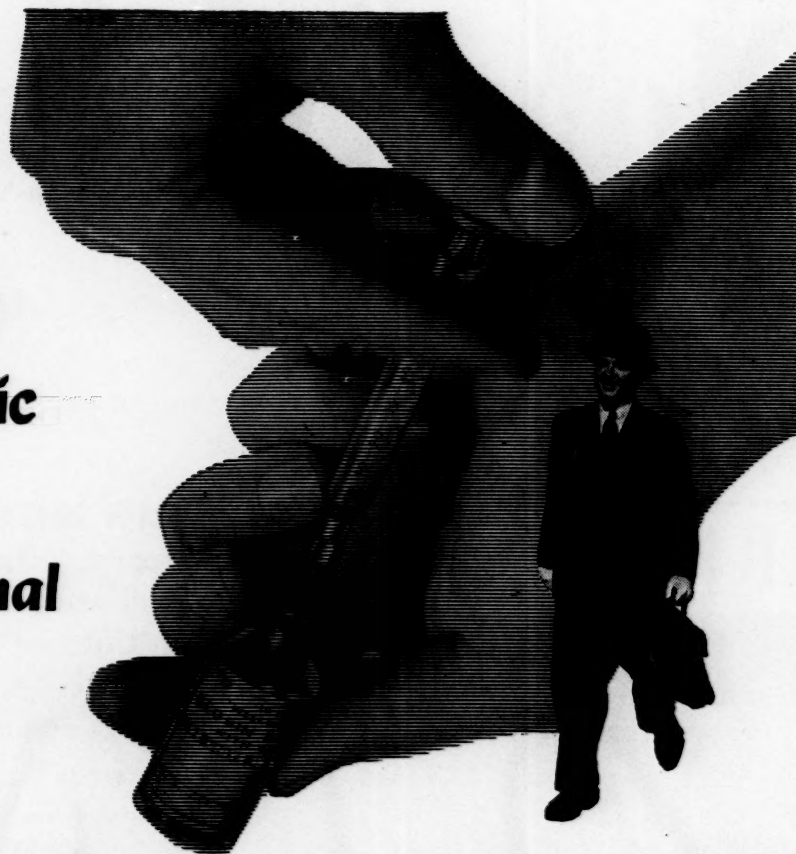
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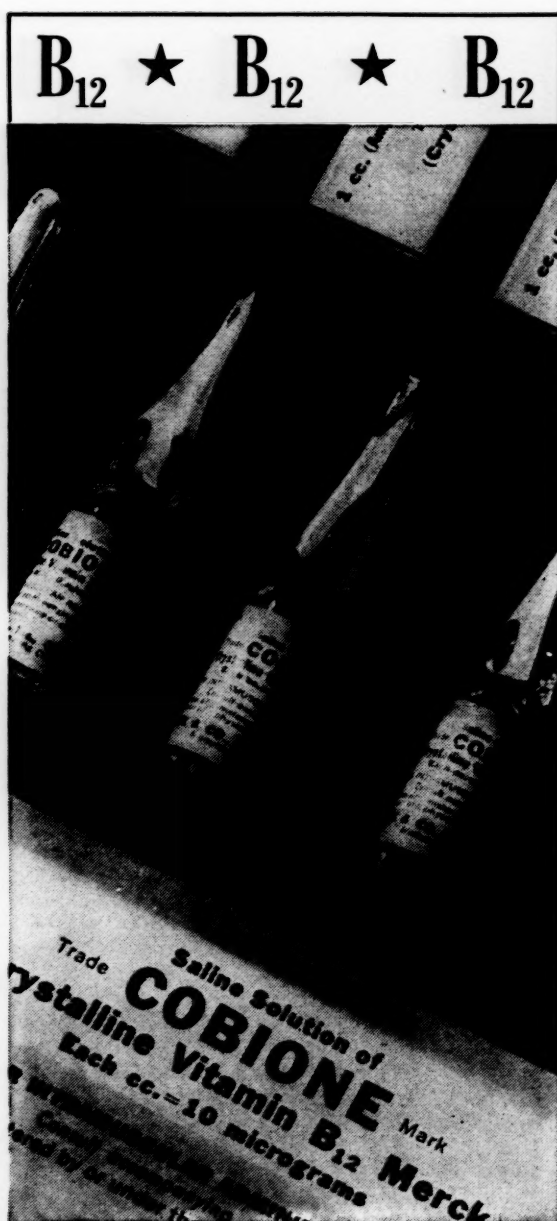
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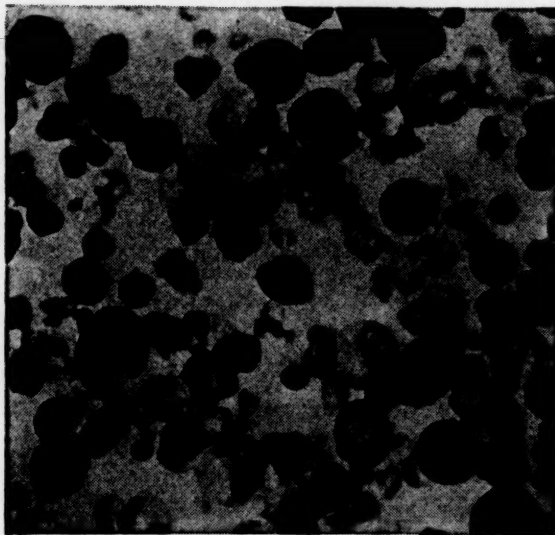
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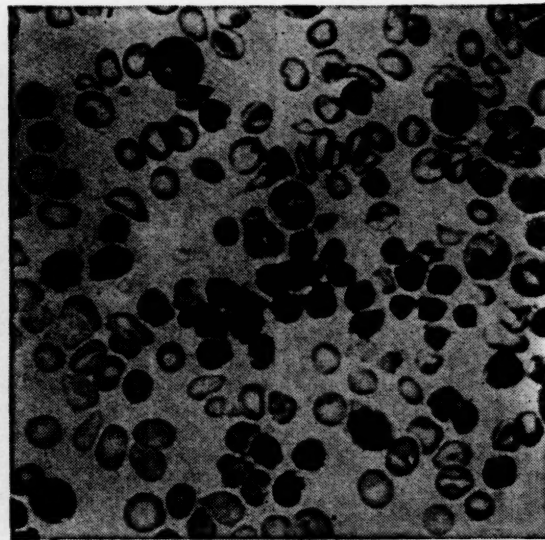
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The American Journal of Medicine

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Editorial

Problems of Hepatic Disease

THE great pandemic of hepatitis involving millions of persons during and following World War II is probably the greatest factor in stimulating the current intense interest in disorders of the liver. Clinicians are being confronted more frequently than ever with baffling problems in the differentiation of this disease from other conditions causing jaundice, especially those requiring surgical intervention, as well as in the recognition of progressive subclinical inflammatory processes and of residual disability which require proper management.

Similar problems are raised by the increasing exposure of large numbers of our population to substances which are potentially injurious to the liver, such as organic solvents, industrial fumes, insecticides and some of the newer medications. It would be truly a great advance if the toxic effects of these agents could be evaluated before irreparable damage has taken place.

There is the challenge, too, presented by that formidable group of mortals who depend somewhat too heavily upon ethanolic solace. The hepatotoxic effects of alcohol vary markedly in different subjects and it is deplorable that the protruding abdomens and dilated veins of the susceptible few force the physician into warning generalities for want of methods to evaluate the tolerance factors of the individual.

Problems such as these have aroused a wholesome spirit of inquiry as to the significance and reliability of the various function tests that may be applied to the

detection of impaired hepatic physiology. Current medical literature abounds in conflicting reports by well trained observers which serve but to emphasize the intrinsic complexities of the problem. Agreement is general, however, that no single test has yet been devised which can be used as an infallible index of the nature or extent of hepatic derangement. The limitations of liver function tests are due in part to the fact that the same disease entity, such as hepatitis or neoplasm, may affect sometimes one and sometimes another portion of the hepatic unit but chiefly because the activities upon which our tests are based are still beyond our mechanistic comprehension.

In a sense, the liver is not a single organ and for the sake of clarification may be regarded in the light of at least four aspects:

First, it stands as a vascular maze through which the portal blood must pass before it joins the systemic circulation. Only recently have methods been devised to estimate the total blood flow through the liver in health and disease, but maldistribution of blood within the organ due to sinusoidal dilatation or constriction, swelling of parenchymal cells, compression due to intrahepatic tension, inflammation or scarring of the portal areas, passive congestion, etc., must be recognized chiefly by clinical inference since no tests are yet available to evaluate such circulatory variables. These may exert a profound effect on the function and even viability of the hepatic tissues.

Second, about one-third of the entire hepatic mass is composed of Kupffer cells,

reticulum and other tissues stemming from the mesenchyme. Thus it stands second only to bone marrow as a reticulo-endothelial organ and like the spleen, lymph nodes, etc., often is affected by diseases involving this important system.

Third, it is an excretory organ. Bile, composed of substances removed from the blood by hepatic activity or synthesized by the parenchymal cells, takes origin within the biliary capillaries which are in essence spaces among the clusters of polygonal cells. Only after these small tracts emerge from the lobule and coalesce to form delicate ducts do they constitute a separate anatomic unit, namely, the biliary tree. Widespread lesions in the periphery of the hepatic lobules, as is occasionally observed in hepatitis and infectious mononucleosis, may cause disruption of these friable structures with the production of jaundice without necessarily impairing the general functions of the liver.

Fourth, and most difficult of all to evaluate by exact measurements, are the intricate metabolic activities of the parenchymal cells which regulate the disposal of almost all foodstuffs and their by-products according to the nutritive requirements of the entire organism. These activities are usually ascribed to integrated enzyme systems but the mechanisms by which balances are maintained are not known. Certain determinations, for example the cholesterol-cholesterol ester content of the serum or the serum albumin, empirically reflect two metabolic equilibria maintained by the liver which are altered in characteristic patterns in certain diseases. Most of the routine metabolic tests for liver function are relatively insensitive and when modifications are introduced to overcome these disadvantages intercurrent variables not pertaining directly to the liver may lead to serious errors.

The clinical appraisal of liver disorders depends upon careful evaluation of the aforementioned factors, such as the extent of portal hypertension, the degree of biliary obstruction, the type of metabolic derange-

ment and the activity of the disease process. It is obvious that the laboratory alone is not yet qualified to give answer to all these considerations; and even when our most reliable tests are properly selected and skillfully integrated with all the clinical features of the disease, an accuracy of diagnosis exceeding 90 per cent can seldom be attained.

Uncertainties and difference of opinion are also widespread in the therapeutic field, especially in regard to dietary management. It has been demonstrated by numerous clinical and laboratory studies that diets low in protein and in lipotropic agents such as choline lead to degenerative changes within the hepatic lobules or to fatty infiltrations which, in turn, render the cells less viable and more susceptible to noxious agents, anoxia and other intercurrent mishaps. The importance of these observations is enhanced by the demonstration of Patek and his associates that the downward trend in a fair proportion of cases of Laennec's cirrhosis can be arrested and actually reversed by a high protein diet rich in vitamin supplements. This significant contribution has led to widely held misconceptions that diet is all-important in the management of hepatic disease in general. Furthermore, the observations of toxicologists and experimental nutritionists on the protective action on the liver of certain accessory factors in the diet of malnourished animals or those exposed to toxic agents has given rise to widespread clinical employment of such substances as methionine, choline, crude liver, vitamin K, tocopherol, pyridoxine, human albumin and protein hydrolysates, in a haphazard array of hepatopathies ranging from acute yellow atrophy to cases of palpable Riedel's lobes. Low fat, high protein diets are also being routinely enforced irrespective of the underlying disorder, a practice which often causes no improvement and may actually add to the emaciation and debilitation of the patient. The experience of many observers indicates that the therapeutic effectiveness of diet in hepatic disease bears a close rela-

tionship to the degree that malnutrition has served as a precipitating or contributing factor. Usually, as long as the patient relishes and digests an adequate, well balanced diet little is to be gained by distorting the menu, and supplements are rarely indicated unless food intake is inadequate or when persistent fatty infiltration of liver cells is demonstrable. Further critical studies on the indications and limitations of dietary regulation in various types of liver disease are very much indicated.

Adequate rest is often neglected as a therapeutic measure. Fatigue and muscular exertion increase the metabolic demands on the liver and depress many of its functional capacities. The recent studies of Bradley indicate that exercise and even upright posture decrease the portal blood flow significantly. When the intralobular circulation is already impeded by disease, the possibility that physical activity may further decrease oxygenation and nutrition of the hepatic cells must be recognized. Theoretical considerations such as these are borne out in practice by the frequency of relapse in hepatitis when the patient attempts early ambulation and by the experience that the decompensated cirrhotic subject may show little improvement until enforced rest is instituted.

The pathogenesis of hepatic disease also presents many unanswered problems, especially those dealing with progressive cellular degeneration and scarring. Many cases of

cirrhosis cannot be ascribed with certainty to infection or exogenous toxins or to known dietary deficiencies, and yet once the injury is initiated the process may continue despite all types of medical management.

Despite the many difficulties in making exact studies of the liver and its disorders the field is not static. New hepatic activities are still being described and familiar ones are being re-evaluated by isotope studies and by improved analytic technics. Serial biopsies are now widely employed in the correlation of anatomic lesions with functional derangements and in observation of the course of disease under controlled conditions. Methods for localizing certain enzymatic activities to various parts of the hepatic unit have recently been devised and are being applied to clinical problems. The effect of the newer antibiotics on the hepatotropic viruses is under intensive study. The nature of the changes in the serum protein-lipid complex found in infectious hepatitis and in other inflammatory conditions of the liver is subject to further study from many angles. Splanchnic hypertension is being successfully treated surgically by shunting portal blood into the vena cava; studies on these patients may throw further light on circulatory factors in cirrhosis and other hepatic derangements. Improvement in diagnosis and management can therefore be predicted with confidence in this difficult clinical field.

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Clinical Studies

Correlation of Liver Function and Liver Structure*

Clinical Applications

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THE study of liver diseases has hitherto relied chiefly upon two sources of information: physiologic examination of liver function and morphologic study of necropsy material. In the past thirty years a large number of liver function tests, based on some of the almost innumerable functions of the liver, has been described. However, the diagnostic interpretation of the several tests still involves theoretical and practical difficulties. Recent attempts to use composite liver function tests¹⁻⁴ have somewhat clarified the picture. Nevertheless, there remain many cases in which performance of a multitude of liver function tests does not lead to a definite diagnosis. Correlation of observations at autopsy with clinical and laboratory findings, too, is in many instances unsatisfactory, especially in acute liver damage. Thus, in some instances in which the pathologist reports impressive but localized alterations, such as central and especially focal necrosis, functional and clinical changes may be insignificant whereas in other instances in which the structural changes are inconspicuous but diffuse, liver function is severely impaired.

The results of liver function tests carried out days or weeks before autopsy cannot be expected to correlate closely with the morphologic findings at necropsy. The liver of the cadaver—even if the necropsy is done

shortly after death—may show a quite different morphologic picture when compared with the “living” liver tissue obtained by aspiration biopsy, as we could establish in a few examples in which biopsies were performed a few hours before death. The former showed widespread breakup of the liver cell cords and marked widening of the perisinusoidal tissue spaces not seen in the latter. It was also found that in previously healthy individuals dying instantaneously, e.g., in a crash, the liver tissue spaces were not visible, in contrast to the open perisinusoidal spaces usually seen in persons who died within one hour after an accident. Agonal changes, therefore, may significantly alter the morphologic picture of the liver.^{4a} Consequently the recently expanded use of liver biopsy⁵⁻¹¹ (excision during laparotomy or peritoneoscopy or by needle aspiration) has made possible better correlation of the structural and functional alterations in different stages of liver disease. Such correlation, applied to the interpretation of both morphologic alteration and functional derangement, should lead to improved diagnosis and management in liver disease.

This presentation concerns itself with a study of liver biopsies in relation to four problems: (1) Correlation of different liver function tests with various histopathologic phenomena independent of the underlying

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disease. (2) Clinical classification of liver diseases on a morphologic basis. (3) Evaluation of the practical improvement in the differential diagnosis of liver disease by the addition of liver biopsy to clinical and functional examinations and (4) Combined functional and morphologic evaluation of therapeutic procedures in liver disease.

METHODS IN LIVER FUNCTION TESTS

The results of a series of sixteen liver function tests were correlated in each case with liver biopsy. The tests employed can be classified and interpreted as follows:

Tests Indicating Liver Cell Damage. 1. *Brom-sulfalein retention:* A retention of more than 6 per cent forty-five minutes after the injection of 5 mg. of dye per Kg. of body weight was considered pathologic due to decreased clearance of the blood from the dye.¹² This test is valuable only in the absence of conspicuous jaundice.

2. *Cephalin-cholesterol flocculation:*¹³ A flocculation greater than 1 plus was considered pathologic, indicative of increased gamma globulin and reduced albumin. This test is rather sensitive and of great practical help in the differential diagnosis of jaundice since it is usually negative in extrahepatic biliary obstruction, even with much liver damage, except when there is associated infection.

3. *Thymol turbidity test:*^{14,15} A turbidity of more than 4 units was taken as pathologic. It indicates increase of lipids and of gamma or beta globulins or lipid protein complexes migrating with them, possibly associated with reduction of the albumin fraction.^{15a} This test is a valuable supplement to the cephalin-cholesterol flocculation test.

4. *Albumin-globulin ratio:* In liver disease a ratio of less than 1.2 was taken as evidence of either reduced synthesis of albumin or increased formation of globulin by the reticulo-endothelial system. Obviously other factors, such as loss of albumin in the urine, may affect the ratio.

5. *Hippuric acid excretion:*¹⁶ The inability of the liver to detoxify and excrete as hippuric acid in the urine more than 0.7 to 1.0 Gm. of a 1.7 Gm. dose of sodium benzoate injected intravenously was considered pathologic. This test is of no value in the presence of renal damage. It is of limited value but useful, especially in acute liver disease.

6. *Cholesterol ester-cholesterol ratio:* The inability to esterify more than 60 per cent of the total serum cholesterol was interpreted as liver damage. The commonly used Bloor method¹⁷ does not yield altogether reliable results whereas the method of Schoenheimer and Sperry¹⁸ is rather elaborate for routine examination. Nevertheless, the cholesterol ester-cholesterol ratio is valuable, especially for quantitative follow-up of the degree of liver damage.

7. *Plasma vitamin A:* Levels of less than 15 micrograms per 100 cc. of plasma were taken as signs of blocked release of vitamin A from the liver to the blood in acute liver damage; in chronic liver disease impaired intestinal absorption is an additional factor.¹⁹⁻²¹ Faulty general nutrition is responsible less often for reduced plasma vitamin A level. Consequently, a reduced level may under certain circumstances, be of diagnostic value, especially in following the clinical course of a patient.

8. *Total serum proteins:* Less than 6.0 Gm. per cent was considered abnormal but not necessarily indicative of liver cell damage since other factors (such as loss of protein in urine, or starvation) may cause a low serum protein. This determination aids primarily in establishing the therapeutic protein requirements.

Tests for Marked Interference with Bile Flow. 1. *Fecal urobilinogen:*²² Excretion of less than 10 mg. of urobilinogen per 100 Gm. of feces indicates lack of secretion of its precursor, bilirubin, into the intestine, as seen in biliary obstruction.

2. *Serum alkaline phosphatase:*²³ Values above 4 Bodansky units indicate either reduced biliary excretion of the enzyme into the intestine or increased production within the liver, provided that excess osteoblastic formation in various bone diseases is ruled out. Levels above 15 units usually point to extrahepatic obstruction. Values between 4 and 15 units are found more often in hepatitis or cirrhosis.

3. *Total serum cholesterol:*²⁴ In a jaundiced patient a level above 250 mg. per cent is considered due to reduced biliary excretion, provided other factors of hypercholesterolemia are excluded (e.g., hypothyroidism, pregnancy, nephrosis, xanthomatosis).

Tests for Either Disturbed Liver Cell Function and/or Marked Interference with Bile Flow. 1. *Urinary urobilinogen:* Urinary urobilinogen is normally excreted in amounts of 1 to 3 mg. per day²⁵ or 1 to 3 units in a two-hour sample.²² This quantity is decreased in biliary obstruction

because of decreased formation of urobilinogen in the intestine and subsequent reduced reabsorption. It is increased in the urine in liver damage due to failure of the damaged liver cells to re-excrete the urobilinogen absorbed from the intestine. Urinary urobilinogen is also increased in hemolytic processes. The determination of urobilinogen in the urine is simple and if performed daily may be of great diagnostic value. Incomplete obstruction, as in choledocholithiasis, gives fluctuating values.

2. *Prothrombin time percentage:*²⁶ This is reduced below 85 per cent of normal by inadequate absorption of vitamin K from the intestine and/or reduced synthesis of prothrombin by the liver cells. Only the former condition (as in obstructive jaundice) gives a sustained response to parenteral vitamin K therapy. The therapeutic test may, therefore, under some circumstances aid in establishing liver damage.

3. *Total serum bilirubin:*²⁷ Elevation above 1.2 mg. per cent signifies retention of bilirubin in the blood stream or, more commonly, its regurgitation from the smallest biliary passages into the blood. The determination aids more in following the course of liver disease than in differential diagnosis.

Test for Portal Inflammation. Sedimentation rate: When elevated above 15 mm./hr. in liver diseases, inflammatory changes in the portal triads were assumed, provided that other inflammatory foci were excluded.

Test for Hepatorenal Relation. Serum non-protein nitrogen: Values above 40 mg. per cent may be found associated with liver damage and are then due to increased reabsorption of nitrogenous substances in the renal tubules, provided that primary renal causes are excluded.²⁸ Such pathologic reabsorption occurs more often in toxic hepatitis or biliary obstruction of long duration than in other types of liver disease.

METHODS IN LIVER BIOPSIES

The majority of liver biopsies in this study were procured by means of a Turkel needle²⁹ inserted under local anesthesia through the seventh to ninth right costal interspace in the mid-axillary line. The patient was placed in the left lateral decubitus position with a pillow under the left flank to act as a "gallbladder rest." This approach assured displacement of all viscera and ascitic fluid. The Turkel needle consists essentially of an outer trocar needle

for insertion through the parietes, with an inner serrated trephine which cuts a core of tissue approximately 2 mm. in diameter. A syringe is attached upon removing the trephine needle to aspirate the tissue core. Others have used the Vim-Silverman needle. This study is now being continued with the use of Gillman's technic.⁹

The biopsy material was fixed in Zenker-formalin or Carnoy's solution. Sections were stained with hematoxylin-eosin, Mallory's aniline blue connective tissue stain and Gomori's reticulum fiber stain.

Because of the danger of fatal hemorrhage from this procedure⁷ the following conditions are considered, for the present, as contraindications to liver biopsy; increasing experience may alter this list: (1) Hypoprothrombinemia (prothrombin time percentage under 85); (2) severe cholemia; (3) passive congestion of the liver; (4) systemic hypertension of marked degree; (5) hemorrhagic diseases; (6) atrophic liver (difficulty in engaging liver with needle).

This study includes our experience with 221 needle biopsies obtained in 154 patients and 106 biopsies obtained during laparotomy.

OBSERVATIONS ON CORRELATION OF LIVER FUNCTION TESTS WITH SEVERAL STRUCTURAL PHENOMENA

As presented in detail in another publication³⁰ the following conclusions can be drawn from correlations made out between certain morphologic phenomena and abnormal results of liver function tests. These correlations were obtained by statistical methods without taking into account the diagnosis in each individual case. They represent association of phenomena rather than necessarily cause and effect relationships. (Table I.)

A significant correlation was found between diffuse liver cell damage and bromsulphalein retention, cephalin-cholesterol flocculation, thymol turbidity and albumin-globulin ratio. A lesser degree of correlation was observed with marked elevation of serum bilirubin, reduction of plasma vitamin A and increase in prothrombin time percentage. No correlations were evident between diffuse liver cell damage and total serum protein, alkaline phosphatase, total cholesterol and cholesterol esters, urinary

and fecal urobilinogen, nonprotein nitrogen and sedimentation rate.

Focal necrosis, in sharp contrast to diffuse parenchymal damage, showed little correlation with any of the liver function tests performed.

function tests. Histologically impressive focal necroses, however, may not be mirrored at all by function tests because the surrounding intact liver parenchyma compensates for the damaged cells. Liver diseases with circumscribed lesions, such as

TABLE I
STATISTICAL RELATION BETWEEN LIVER FUNCTION TESTS AND PATHOLOGIC PHENOMENA
WITHOUT REFERENCE TO DIAGNOSIS

	Diffuse Liver Cell Damage	Focal Necrosis	Regener- ation	Distorted Recon- struction	Periportal Inflam- matory Activity	Fatty Metamor- phosis	Kupffer Cell Activity
Cephalin-cholesterol flocculation.....	+++	0	0	+++	±	0	0
Thymol turbidity.....	+++	0	++	++	0	0	0
Reduction of total serum protein.....	0	0	0	0	0	0	0
Abnormal serum albumin-globulin ratio.....	+++	0	0	0	0	0	+++
Elevated serum N.P.N.....	0	0	0	0	0	0	0
Elevated urinary urobilinogen.....	0	0	0	0	0	0	0
Reduced stool urobilinogen.....	0	0	0	0	0	0	0
Elevated total serum cholesterol.....	0	0	0	0	0	0	0
Reduced cholesterol ester ratio.....	0	0	0	0	0	0	0
Serum bilirubin elevated above 8 mg. per cent.....	+	0	0	0	0	0	+++
Bromsulphalein retention.....	+++	0	0	0	0	0	0
Reduced hippuric acid synthesis.....	0	0	0	0	0	0	0
Elevated serum alkaline phosphatase...	0	0	0	0	0	0	0
Reduced prothrombin time percentage...	+	0	0	0	0	0	0
Reduced plasma vitamin A.....	+	0	0	0	0	0	0
Elevated sedimentation rate.....	0	0	0	++	++	0	0

Regeneration of individual liver cells showed a significant correlation with thymol turbidity.

Distorted reconstruction of the lobular pattern, as seen in cirrhosis, revealed a significant degree of correlation with the cephalin-cholesterol flocculation, thymol turbidity and elevation of the sedimentation rate.

Periportal inflammatory activity showed a significant correlation with increased sedimentation rate.

Fatty metamorphosis of the liver was not statistically correlated with any of the liver function tests employed.

Kupffer cell activity was found related to elevated serum bilirubin and pathologic albumin-globulin ratio.

It should be emphasized that diffuse liver cell damage, although morphologically often not conspicuous, is usually associated with markedly abnormal results in many

granulomas, abscesses (e.g., amebic), tumor metastases or other local alterations which do not influence the surrounding liver parenchyma, may not be disclosed by liver function tests.

MORPHOLOGIC CLASSIFICATION OF DIFFUSE PARENCHYMAL LIVER DAMAGE

Although its inflammatory character in many cases is not established, acute parenchymal liver damage, if clinically conspicuous, is referred to as hepatitis. Hepatitis may be classified in two types: primary or medical form due to various infections and intoxications, and a secondary or surgical form due to tumors, scars and strictures involving the biliary tract. In the following enumeration of the most commonly encountered forms the clinical and morphologic findings are summarized and the laboratory tests listed in the order of

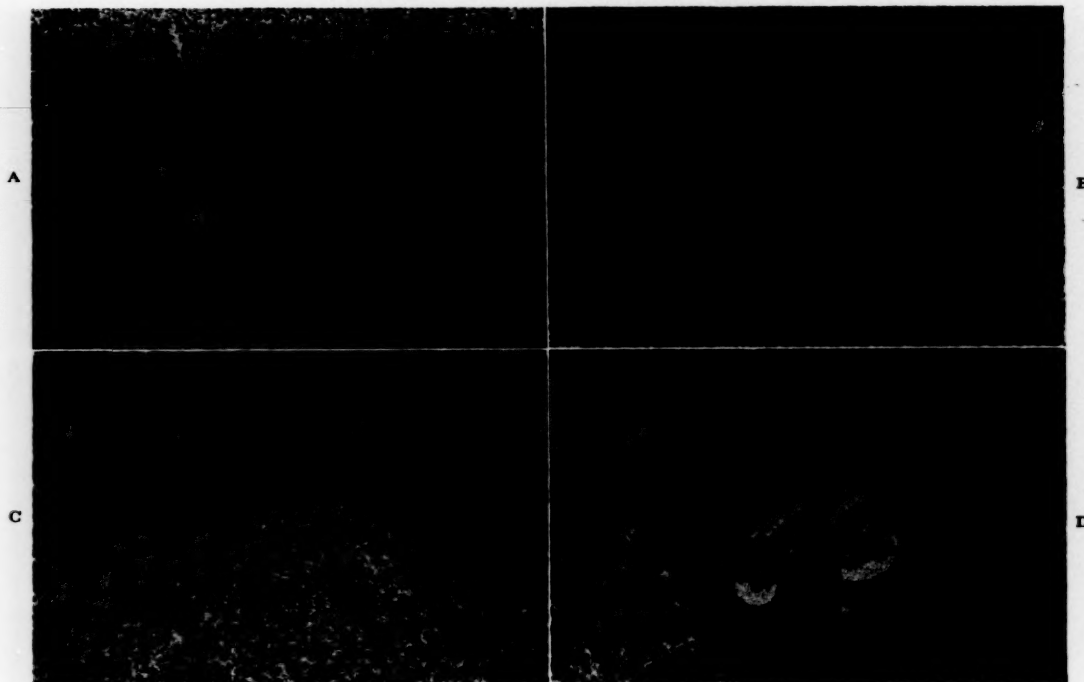


FIG. 1. A, autopsy specimen of an acute fulminating form of viral (infectious) hepatitis. The liver cells have almost completely disappeared except for a few regenerates which simulate proliferated bile ducts. Phagocytosing, chiefly histiocytic, exudate cells are seen in the lobular framework and portal triads. B, biopsy specimen of a severe (non-fatal) form of viral hepatitis. The liver cells are irregularly stained and poorly outlined; occasionally they are hyalinized. The nuclei vary in size. Round cells are seen in sinusoids and in large numbers in portal triads. C, biopsy specimen of mild viral hepatitis. The liver cell cords are irregularly arranged and their cells vary in size. Throughout the parenchyma and portal triads many mononuclear cells are seen. D, biopsy specimen of viral hepatitis with protracted convalescence. The poorly delineated portal triads reveal marked cellular infiltration and early fibrosis. Around them regeneration of liver cells is conspicuous.

significance. However, it is not implied that the results of liver function tests permit a histopathologic diagnosis.

Primary Hepatitis. 1. *Infectious or viral hepatitis:* At least two portals of entry are recognized: an oral route with an incubation period of two to six weeks and a parenteral route (homologous serum jaundice) with an incubation period of two to six months.³⁷ The following main types of this disease are observed:

The fulminant form^{32,33} is often seen in homologous serum jaundice and is fatal in less than ten days after onset of icterus. Histologically, (Fig. 1A) an "explosive" destruction of almost all liver cells is seen with little remaining that resembles the normal liver architecture. There is marked inflammatory reaction and phagocytosis. This is one of the types formerly referred to as "acute yellow atrophy." Most of the

liver function tests are abnormal, especially the cephalin-cholesterol flocculation and thymol turbidity; serum bilirubin, prothrombin time and (usually) urinary urobilinogen are markedly elevated. In addition there is a decrease of plasma vitamin A, hippuric acid synthesis, cholesterol ester-cholesterol and albumin-globulin ratios. The sedimentation rate is increased.

In the prodromal period of the severe (non-fatal) form, often prolonged, febrile or gastrointestinal symptoms predominate. The course is stormy and jaundice usually lasts about four weeks, resulting in considerable weight loss and weakness. Results of the liver function tests are similar to those in the previous form. In addition, the alkaline phosphatase is usually elevated. Histologically, (Fig. 1B) there is diffuse damage of the liver cells with considerable mesenchymal reaction as indicated by diffuse intralobular

and periportal infiltration with phagocytic round cells.

In the mild form jaundice may be absent. It is, therefore, not infrequently missed because of its clinically inconspicuous course. Only a few of the liver function tests are abnormal. There is usually retention of bromsulfalein, increase of urinary urobilinogen and increase in the sedimentation rate. Cephalin-cholesterol flocculation and thymol turbidity may be abnormal. In addition hippuric acid synthesis and cholesterol esters are occasionally reduced. Liver biopsy (Fig. 1c) shows diffuse but milder liver cell damage and not very conspicuous intralobular and periportal mesenchymal reaction.

In the protracted stage icterus is usually absent and symptoms of fat intolerance and neurasthenia predominate. A transition to cirrhosis may occur. Only the thymol turbidity and sedimentation rate may be abnormal. Liver biopsy (Fig. 1d) often reveals more than anticipated from the clinical picture. Liver cell damage is slight but signs of regeneration of parenchymal cells with portal fibrosis and round cell infiltration suggest a chronic phase of the disease.

Absence of bile from the duodenum may occur in any stage of hepatitis, leading to a clinical syndrome similar to extrahepatic biliary obstruction. Serum bilirubin, total cholesterol, alkaline phosphatase and sedimentation rate are high while the urinary and fecal urobilinogen are markedly decreased. Results of the other function tests will depend on the type of hepatitis associated with this phenomenon. In the acute stage they are usually abnormal; in the late, protracted form of viral hepatitis (transition into cholangiolitic cirrhosis of Hoffbauer and Watson³⁴) they may be normal. There is no characteristic histologic picture for the intrahepatic biliary arrest *per se*. Morphologically, the picture will depend on the stage of hepatitis, independent of the arrest of bile flow.³⁵

2. *Toxic hepatitis*: This comprises conditions caused by substances known to be in-

jurious to the liver such as exogenous agents (chemicals, drugs and bacteria such as pneumococci, salmonella) or endogenous toxins (e.g., in pregnancy, hyperthyroidism, etc.). In a large number of patients with morphologically identical lesions no hepatotoxic factor can be elicited in the history.

In the fatal form prodromal symptoms are variable but the course is stormy and rapid with death in cholemia and uremia. Most liver function tests give abnormal results. However, the cephalin-cholesterol flocculation and thymol turbidity tests are not always positive. Prothrombin time, serum bilirubin, urinary urobilinogen, non-protein nitrogen and sedimentation rate may be increased. Albumin-globulin and cholesterol ester ratios and plasma vitamin A are decreased. Histologically, in the most common form, there is widespread necrosis of liver cells in the central zone (Fig. 2A) without much evidence of mesenchymal reaction. This picture is often referred to as central necrosis.

In the severe (non-fatal) form the prodromal symptoms may be prolonged. The clinical course and results of liver function tests are similar to those in the fatal form but the patient recovers slowly. Morphologically, (Fig. 2B) gradual cell death and disappearance of liver cells occurs in zonal arrangement, usually in the center of the lobule, but little mesenchymal reaction is noted.

The fatty form is frequently called fatty degeneration and is often the result of a known hepatotoxic substance, at times predisposed by nutritional deficiency. Results of the liver function tests are similar to those in the two previous forms of toxic hepatitis. Liver biopsy (Fig. 2c) shows diffuse fatty metamorphosis with necrobiosis of liver cells without marked mesenchymal reaction.

In the mild form there is no characteristic prodromal state and the clinical course is characterized by prolonged, often mild jaundice. Urinary urobilinogen is high and serum bilirubin slightly increased. There is retention of bromsulfalein. The flocculation tests may be positive. In addition hippuric

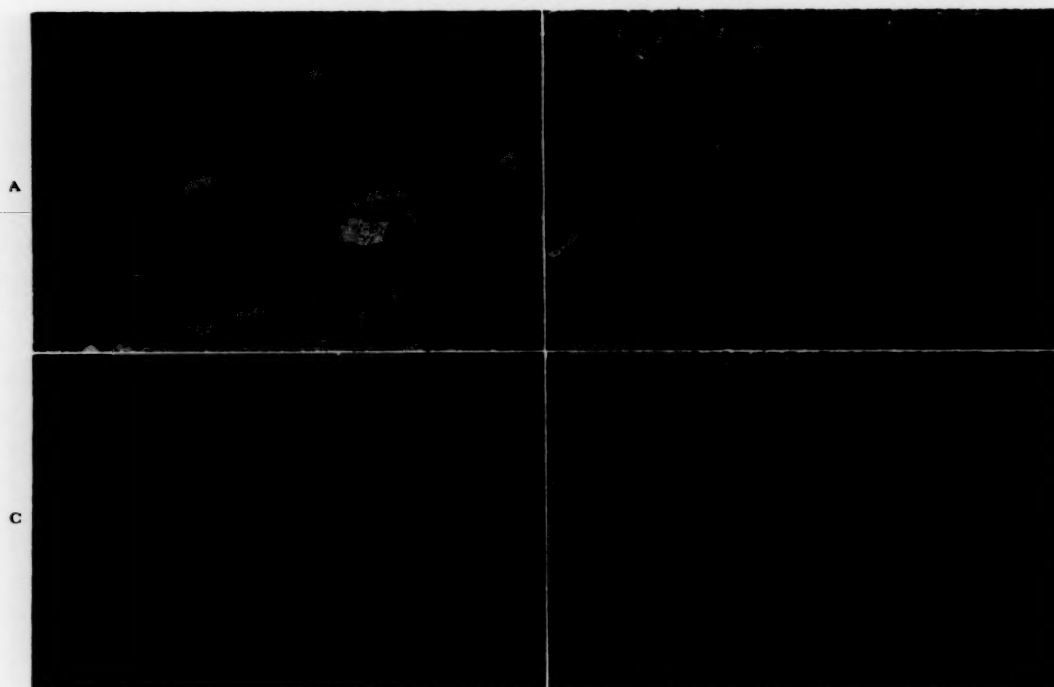


FIG. 2. A, autopsy specimen of toxic hepatitis. The liver cells in the lobular centers have disappeared and the cells on the border of the denuded areas are necrobiotic. Little mesenchymal reaction is seen. B, biopsy specimen of severe (non-fatal) toxic hepatitis. There is coagulation necrosis and vacuolization of epithelial cells in the center of the lobules, with moderate regeneration and little mesenchymal reaction. C, biopsy specimen of fatty toxic hepatitis. There is extensive fatty metamorphosis with coagulation necrosis, necrobiosis and bile pigment imbibition of liver cells. The Kupffer cells are hardly mobilized. D, biopsy specimen of mild toxic hepatitis. The staining qualities of the liver cells are irregular throughout. Liver cell cords and portal triads are almost devoid of cellular reaction.

acid synthesis and cholesterol ester ratio may be decreased. In the liver biopsy (Fig. 2D) diffuse or centrilobular damage is seen, mild in degree, associated with focal necrosis with almost no mesenchymal response.

Secondary Hepatitis. In secondary hepatitis occurring in surgical conditions of the biliary tract caused by tumors, stones or strictures, liver damage is due either to prolonged biliary obstruction (biliary hepatitis) or to bacterial infection of the portal triads (purulent hepatitis).

1. *Biliary hepatitis:* Liver cell damage with impaired function is due to biliary stasis. The extent of biliary hepatitis depends on the degree and duration of the obstruction. It is, therefore, rather common in malignant obstruction of the bile ducts which is usually complete and permanent.

The early form occurs in the first weeks of obstruction and may be associated with pruritus. Fecal and urinary urobilinogen

are absent while serum bilirubin, alkaline phosphatase, total cholesterol, prothrombin time and sedimentation rate are increased. The thymol turbidity is slightly increased but the cephalin-cholesterol flocculation test is negative. Liver biopsy (Fig. 3A) shows bile stasis and bile impregnation of the liver cells in the center of the lobules with slight liver cell damage.

The advanced form is usually the result of several weeks of complete biliary obstruction. The patient is cachectic, has acholic stools, at times a palpable gall-bladder and may be cholemic. The same tests are positive as in the earlier stage. In addition there is reduction of hippuric acid synthesis, of total protein, of albumin-globulin and cholesterol ester ratios; non-protein nitrogen is often increased. Biopsy (Fig. 3C) reveals bile casts in the central and peripheral portions of the lobule with a significant degree of diffuse liver cell damage and circumscribed necroses with

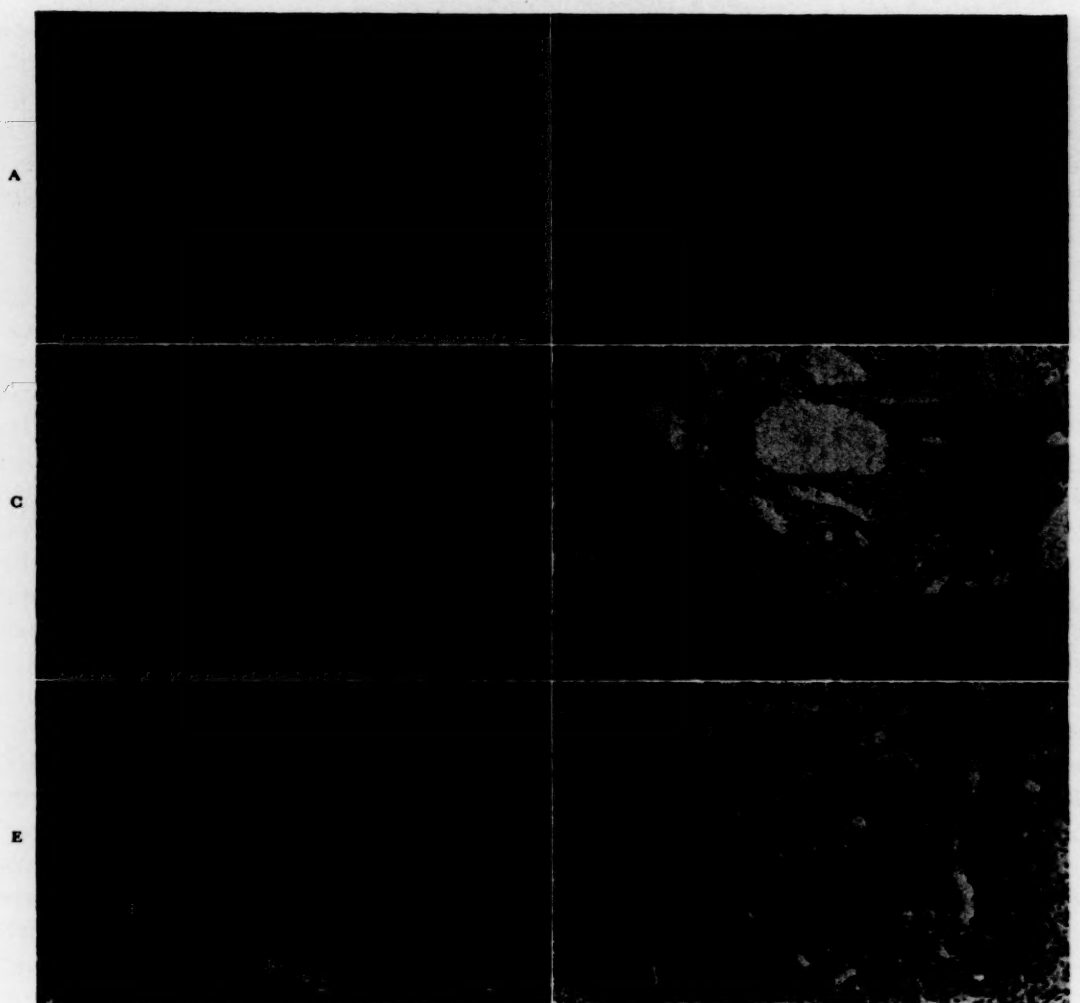


FIG. 3. A, biopsy specimen of early biliary hepatitis. There are bile thrombi in the center of the lobules, with little liver cell damage in the adjoining areas and almost no mesenchymal reaction. B, biopsy specimen of a case of portal perilymphangitis. Lymphocytes and histiocytes are seen around lymphatics of the portal triads. Bile ducts, vessels and liver parenchyma reveal no abnormal changes. C, biopsy specimen of severe biliary hepatitis. Bile thrombi are seen in central and periportal areas of the lobule. There is diffuse liver cell damage and enlargement of the portal triads due to circular fibrosis. D, biopsy specimen of purulent hepatitis showing perilymphangitic accumulations of round cells and polymorphonuclear cells in enlarged portal triads. The latter are not sharply limited and reveal bile duct proliferation. E, biopsy specimen of a chronic form of biliary hepatitis. Proliferated connective tissue with bile ducts surround the parenchyma in which distorted reconstruction has started. Some liver cell damage is noted. F, biopsy specimen of a chronic form of purulent hepatitis. There is dense cellular infiltration of the enlarged and fibrosed portal triads which reveal proliferating bile ducts. The liver parenchyma shows little damage.

bile imbibition (bile infarcts). The periportal fields show circular fibrosis.

The chronic cirrhotic form represents the late stage of an obstruction, usually malignant, with dark green icterus, pruritus, cachexia, anemia, large liver, occasionally palpable gallbladder but rarely ascites. The same tests are positive as in the preceding forms and plasma vitamin A is also reduced. Morphologically, (Fig. 3E) there is portal

fibrosis, bile stasis and partially distorted reconstruction of the lobular pattern. Usually liver cell damage is marked.

2. *Purulent hepatitis*: Bacterial infection of the portal triads develops through hematogenous, hemolymphatic or cholangitic routes. It occurs in various inflammatory lesions in the portal system independent of degree or duration of biliary obstruction. It may, therefore, complicate any stage of

surgical jaundice, but most often the benign form.

The perilymphangitic form may occur in any intra-abdominal condition in which irritating material reaches the liver, e.g., in cholecystitis without jaundice or other gastrointestinal lesions. The clinical picture is not characteristic. The sedimentation rate is usually increased. Biopsy of the liver (Fig. 3B) shows accumulations of round cells and occasional polymorphonuclear leukocytes around the lymphatics of the portal triads, frequently without evidence of liver cell damage.

The suppurative form is clinically characterized by chills, fever and leukocytosis, as seen with cholangitis or Charcot's intermittent hepatic fever. In contrast to the biliary form the cephalin-cholesterol flocculation and thymol turbidity tests are both positive. Serum bilirubin is not always elevated, there is bromsulfalein retention, increase in urinary urobilinogen and sedimentation rate and usually reversal of the albumin-globulin ratio. In more severe cases the cholesterol ester ratio, hippuric acid synthesis and plasma vitamin A are reduced. Biopsy (Fig. 3D) reveals multiple purulent foci or abscesses in the portal triads and diffuse liver cell damage.

The chronic form is usually seen clinically after prolonged incomplete obstructive jaundice in the presence of inflammation, e.g., from a stricture of the bile ducts. There are bouts of chills, fever and leukocytosis with development of a large firm liver, large spleen and anemia. The cephalin-cholesterol flocculation and thymol turbidity tests are positive. Serum bilirubin, urinary urobilinogen, prothrombin time and sedimentation rate are increased; the total serum protein is reduced. In addition there is a decrease in the albumin globulin ratio, plasma vitamin A, cholesterol ester ratio and hippuric acid synthesis. Morphologically, (Fig. 3F) there is portal fibrosis with dense infiltration by inflammatory cells. Liver cell damage is evident. The lobular pattern shows some distorted reconstruction.

Cirrhosis. This is a group of chronic liver

diseases or hepatitides of varying etiology. Connective tissue proliferation and distorted reconstruction of the lobular pattern resulting in more or less portal hypertension are significant features. Some types are related to the forms of hepatitis already described.

1. *Portal Cirrhosis without Jaundice.* This is the type originally described by Laennec. Its etiology is as yet unestablished although nutritional deficiencies with or without alcohol addiction seem to play a rôle. There is an insidious onset and in later stages, subicterus, ascites, esophageal varices, spider nevi, splenomegaly and anemia appear. The albumin-globulin ratio and total serum protein are decreased. There is bromsulfalein retention. The cephalin-cholesterol flocculation and thymol turbidity tests are often positive. The sedimentation rate and urinary urobilinogen are increased. In addition hippuric acid synthesis may be reduced. Biopsy (Fig. 4A) reveals a progressive portal fibrosis, distorted reconstruction—often complete—of the lobular pattern usually without marked liver cell damage.

2. *Portal Cirrhosis with Jaundice.* Here the clinical picture is complicated by icterus and occasionally even by cholemia. In addition to the abnormal liver function tests there is a marked increase in serum bilirubin, prothrombin time and usually non-protein nitrogen. In addition the cholesterol ester ratio, hippuric acid synthesis and (often) plasma vitamin A are reduced, the serum alkaline phosphatase is elevated. Morphologically, (Fig. 4B) in addition to the histologic picture of portal cirrhosis just described, the liver cells in the nodules are found to be diffusely damaged and there are many bile casts. Occasionally a cholestatic phase occurs in this form, characterized by absence of urobilinogen from urine and feces, by high total cholesterol and extremely high alkaline phosphatase. In this phase encircling fibrosis around the small bile ducts and severe bile stasis is noted histologically.

3. *Fatty Cirrhosis.* This is now considered the result of a nutritional deficiency (ab-

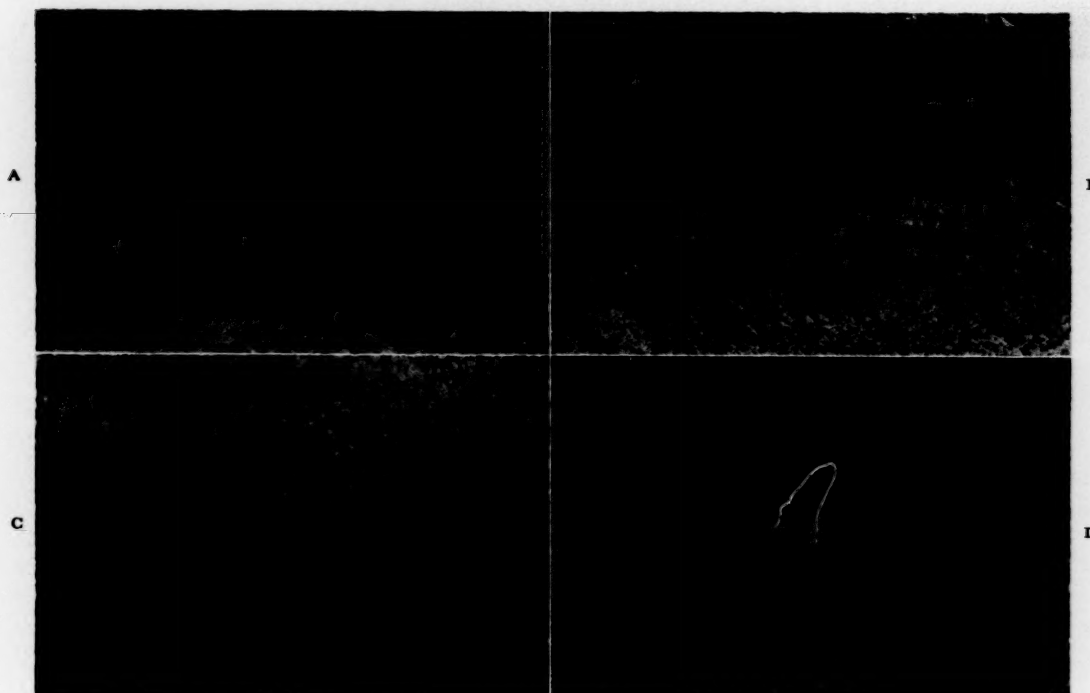


FIG. 4. A, biopsy specimen of portal cirrhosis without jaundice. Nodules of a variable size contain almost intact liver cells. The nodules are surrounded by narrow connective tissue bands, with cellular infiltration and proliferating bile ducts. B, biopsy specimen of portal cirrhosis with jaundice. The nodules are not sharply demarcated from the connective tissue bands. The liver cells reveal diffuse damage, are dissociated and surround bile casts. C, biopsy specimen of fatty cirrhosis. The liver cells are arranged in nodules of relatively uniform size which are separated by sharply delineated narrow trabeculae. The cells usually contain one large fat droplet. D, biopsy specimen of postnecrotic cirrhosis after viral hepatitis. Various sized nodules are surrounded by wide connective tissue bands containing cord-like liver cell regenerates simulating proliferating bile ducts in addition to vessels and partially phagocytosing mononuclear cells.

sence of lipotropic substances), seen often in alcoholics and characterized clinically by a large liver, slight portal hypertension, subicterus and slight anemia. There is bromsulfalein retention, reduced serum protein and lowered albumin-globulin ratio. Urinary urobilinogen is slightly increased. The cephalin-cholesterol flocculation and thymol turbidity tests may or may not be positive. In some cases the sedimentation rate is increased and the cholesterol ester ratio reduced. Biopsy (Fig. 4c) reveals diffuse fatty metamorphosis and beginning distorted reconstruction of the lobular pattern but little evidence of liver cell necrosis.

4. *Postnecrotic cirrhosis.* This is thought to be the sequel of chronic viral hepatitis or, less commonly, of toxic hepatitis. The clinical picture is that of cirrhosis (portal hypertension, anemia and spider nevi) with more or less severe jaundice. The cephalin-

cholesterol flocculation and thymol turbidity tests are positive, serum bilirubin, prothrombin time and urinary urobilinogen

TABLE II
IMPROVEMENT IN DIAGNOSIS OF LIVER DISEASES BY THE USE
OF A SERIES OF LIVER FUNCTION TESTS AND LIVER BIOPSY

Final Diagnosis	No. of Cases	Percentage of Correct Diagnoses Based on		
		Clinical Observation	Clinical Observation Plus Liver Function Tests	Clinical Observation, Liver Function Tests and Biopsy
Infectious hepatitis.....	29	86	90	93
Toxic hepatitis.....	35	57	68	91
Cirrhosis with jaundice....	52	77	92	98
Cirrhosis without jaundice..	18	83	94	100
Benign obstruction.....	27	55	85	89
Malignant obstruction.....	31	74	96	96

are elevated. The total serum protein is reduced and the albumin-globulin ratio is reversed. There is also a reduction of

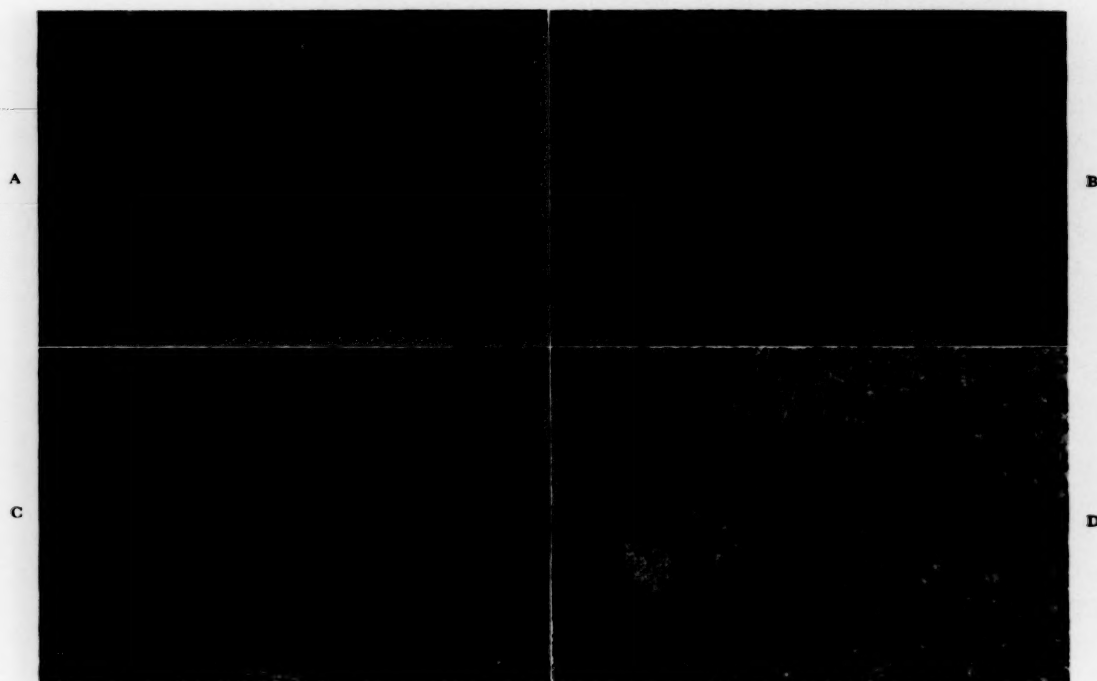


FIG. 5. A, biopsy specimen from a patient with hepatomegaly which proved to be due to amyloidosis. Extensive deposits of pinkish-staining amyloid separate the sinusoids from the compressed liver cell cords. The liver cells themselves reveal little changes. B, biopsy specimen from a patient with Boeck's sarcoidosis. A tubercle is seen composed of epithelioid cells in palisade arrangement, with preserved capillaries in the center and lymphocytes in the outer zone. C, biopsy specimen from a patient with lymphosarcoma. Accumulations of lymphoblastic elements surround vessels and bile ducts in the portal triads. The cellular accumulations are well delineated from the liver parenchyma. D, biopsy specimen of a metastatic adenocarcinoma. The tumor compresses the liver cell cords in the center of which bile thrombi may be seen.

plasma vitamin A, cholesterol ester ratio and hippuric acid synthesis. The sedimentation rate is elevated. Morphologically, (Fig. 4D) the connective tissue in wide areas appears collapsed after the disappearance of liver parenchyma due to extensive necrosis. Otherwise, there is more or less diffuse reconstruction of the lobular pattern with progressive liver cell damage.

LIVER FUNCTION TESTS AND LIVER BIOPSY AS AN AID IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE AND/OR HEPATOMEGALY

The combination of liver function tests with clinical observations and simple urinalysis raises considerably the percentage of correct diagnoses of liver diseases with jaundice. In a previous report³⁶ on 563 jaundiced and 112 non-jaundiced patients use of the liver function tests improved the percentage of correct diagnoses from 62 per cent at the time of the first examination of

the patients to 95 per cent after complete clinical and laboratory work-ups. In this series 192 cases were available in which the diagnosis considered final on discharge or death of the patient was compared with (1) the impression obtained from clinical examination only, (2) the diagnosis derived from clinical observation plus the results of liver function tests and (3) the diagnosis based on biopsy findings together with the just mentioned data. (Table II.) In almost all types studied accuracy of the diagnosis was improved by the liver function tests. Liver biopsy was of additional help. The improvement in diagnosis was greatest in toxic hepatitis. In 5.3 per cent of all cases the histologic diagnosis of the biopsy specimen differed from the final diagnosis and was, therefore, probably wrong.

In some conditions associated with hepatomegaly but without disturbance of liver function, jaundice or ascites, the nature of

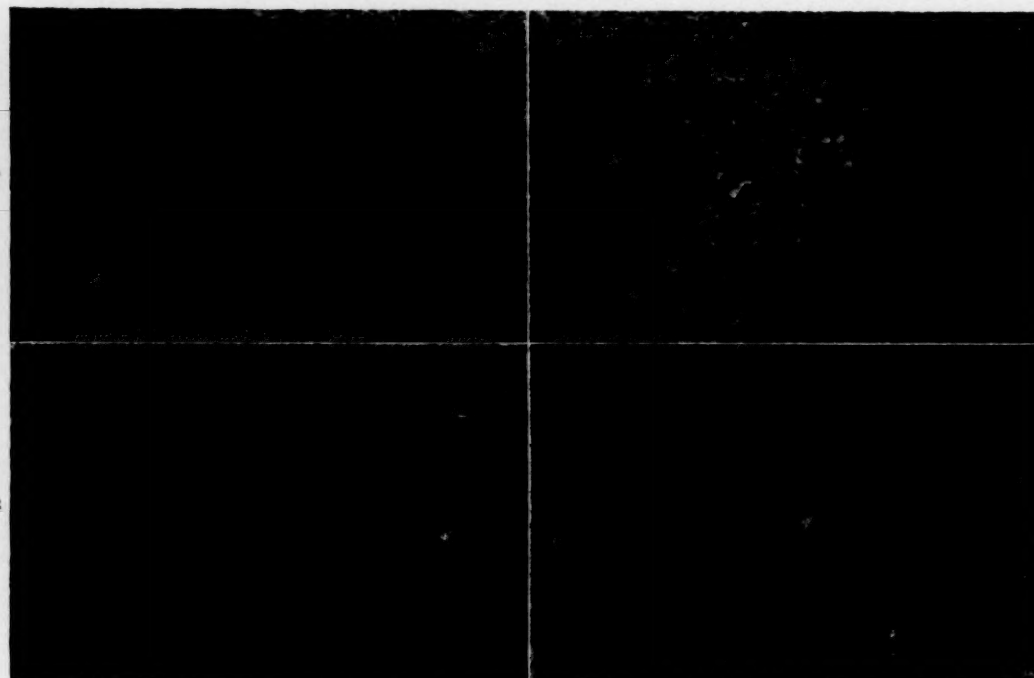


FIG. 6. A, biopsy specimen from a patient with early fatty cirrhosis before lipotropic therapy. Jaundice and hepatosplenomegaly were present; liver function tests were abnormal. Extensive fatty metamorphosis and bile thrombi can be seen; B, biopsy specimen from the same patient as A four weeks after lipotropic therapy. The liver function tests were improved. The liver cells are now fat-free and show signs of cellular regeneration. However, cirrhotic changes such as increased connective tissue with cellular infiltration and proliferating bile ducts are now conspicuous. C, biopsy specimen from a patient with recovering viral hepatitis before start of exercise. Moderate degree of liver cell damage and mesenchymal reaction is present. D, biopsy specimen from the same patient as C taken after three days of controlled exercise. Increase in liver cell damage and mesenchymal reaction is noted. Some liver function tests also showed regression.

the hepatic involvement can be recognized by liver biopsy. In the following instances of this group the diagnosis was first made on the basis of biopsy findings: (1) Amyloidosis (Fig. 5A); (2) Boeck's sarcoidosis (Fig. 5B); (3) lymphosarcoma (Fig. 5C); (4) primary carcinoma of the liver; (5) metastatic carcinoma (Fig. 5D).

This method of diagnosis can also be expected to be of diagnostic help in various storage diseases and in granulomatous or parasitic lesions of the liver.

HISTOLOGIC EVALUATION OF THERAPEUTIC PROCEDURES IN LIVER DISEASES

Evaluation of the morphologic changes occurring after the application of various therapeutic agents may supplement information obtained from clinical and laboratory studies in the human. This help is most valuable since relatively few therapeutic

principles in liver diseases are well established and since clinical and laboratory results are sometimes contradictory.

In addition to the well established principle of administration of a diet of high carbohydrate, high protein, low fat (in acute infectious hepatitis fat may be given as tolerated since the liver is poor in fat) and high vitamins, the intake of methionine (as free amino acid or in protein) or of choline (with or without cystine) has been recommended in recent years.³⁷⁻³⁹ These substances are essential in removal of fat from the liver (lipotropic activity)⁴⁰ by providing labile methyl groups. To methionine, which may be formed in the body from choline and cystine, has also been ascribed a detoxifying effect by providing sulfhydryl groups.⁴¹

While biopsy studies in the human provide additional evidence for the lipotropic

effect of this treatment of fatty livers of various etiology,⁴² they do not necessarily prove that lipotropic therapy is a cure for cirrhosis. In some instances, despite fat removal, the inflammatory process in the portal triads may progress. (Figs. 6A and B.)⁴³

That bed rest is an important adjuvant in the treatment of hepatitis—particularly the infectious type^{44,45}—is emphasized by the marked deterioration of the histologic picture of the liver even in the recovery stage if a biopsy is repeated after exercise. (Figs. 6c and d.)

SUMMARY

1. An attempt has been made to illustrate the aid in diagnosis and management of liver diseases derived from the use of liver function tests and liver biopsy findings, and correlations between them.

2. The significance of a series of liver function tests and the indications and contraindications of liver biopsy in liver disease and other hepatomegalies are briefly discussed.

3. Correlation between morphologic and functional findings helps in evaluation of liver function tests and reveals that most liver function tests give abnormal results in diffuse parenchymal diseases whereas in focal alterations, regardless of severity, none or only a few tests may be pathologic.

4. Based on morphologic and functional criteria, acute hepatic damage was subdivided into viral, toxic, biliary and purulent types; different forms in each group were illustrated by clinical, laboratory and morphologic criteria. The various forms of cirrhosis were similarly discussed.

5. The improvement in diagnosis of liver diseases derived from use of liver function tests and the additional help of liver biopsies is demonstrated. Liver biopsy also can be applied to the critical evaluation of therapeutic procedures in hepatic disease.

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The Correlation of Hepatic Structure and Function*

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THE wave of enthusiasm for the performance of liver biopsy as a routine diagnostic procedure dates from the demonstration by Iverson and Roholm¹ that the technic is simple, relatively safe when carried out with proper attention to detail and provides a piece of liver tissue of sufficient size to permit of serious histologic study. Hoffbauer² published an excellent review of the evolution of the procedure to date in which he considers the advantages and disadvantages of various technics. He believes, as we do, that the Vim-Silverman needle technic, as originally described by Tenopyr and Silverman³ and by Tripoli and Fader,⁴ is safe and efficient. All specimens considered in this study were obtained by this method. Only an anterior approach has been used and biopsy has been limited to patients with palpable livers. In the course of more than a hundred such biopsies no mishaps have occurred.

Histologic evaluation of these specimens in this clinic constitutes one part of a broad program of investigation of the normal and abnormal clinical physiology of the liver. In this report we shall attempt to correlate biopsy, clinical and biochemical findings in selected patients studied under controlled conditions. In attempting such correlation we have indulged in purposeful oversimplification of an extremely complex problem.

CLINICAL MATERIAL

A large group of patients with acute, subacute and chronic liver disease has been followed clinically, chemically and histologically over prolonged periods of time. The acute group has included individuals with all degrees of severity of "epidemic viral" and "homologous serum" hepatitis. Of those men with subacute (obviously a relative term) forms of hepatic involvement the majority have represented cases of non-resolving viral hepatitis but at least two men have had long-continued cholangitis referable to coccal and/or bacillary infection.

The patients with chronic liver disease, i.e., "cirrhosis," have had, with only one exception, a history of use and abuse of alcohol over fifteen or more years. The majority have been in the fourth decade.

For the purposes of this report three acute, one subacute and five chronic patients have been arbitrarily selected from the larger group as being most carefully studied and most representative.

STUDIES

Clinical Criteria. In the clinical evaluation of these patients, certain objective entities have been carefully recorded for comparative purposes: (1) general nutrition; (2) apparent degree of scleral icterus;

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(3) liver size, as noted at the right anterior axillary line (cm. below the rib margin); (4) degree of splenomegaly, if present; (5) venous dilation—chest, abdomen and back; (6) spider angiomas; (7) degree of ascites, if present; (8) degree of dependent edema, if present; (9) evidence of "vitamin B deficiency" as manifested by abnormalities of the tongue, skin and mucous membranes; (10) status of appetite, particularly in relation to therapy; (11) gynecomastia, if present; (12) fetor hepatis if present. In the text gradation of positive physical findings are arbitrarily recorded on a 1+ to 4+ basis.

Histology. Initially the entire specimen obtained from the Vim-Silverman needle—a cylinder of tissue 2 mm. in diameter and varying from 1 to 3 cm. in length in the fresh state—was fixed in formalin and stained with hematoxylin and eosin. As our technic improved and the usual specimen approached the 3 rather than the 1 cm. length the tissue was divided, half being placed in formalin and half in absolute alcohol for later staining with Best's carmine. Other stains, including osmic acid, Sudan III and prussian blue (for iron pigment), have also been used. With few exceptions, as will be noted below, the hematoxylin and eosin, and carmine preparations gave us as much or more information than we were able to obtain with other technics.

Chemistry. In an organ such as the liver with (normally) such homogeneity of cellular structure and such extreme multiplicity of chemical activities, it would at first glance seem almost a hopeless task to set up any system of chemical evaluation which could be correlated well with structural alteration.

In our chemical panel we have attempted to include quantitative or semi-quantitative procedures which would give some information concerning: (1) the excretory-detoxification mechanisms (icterus index, free and combined bilirubin blood levels, bromsulfalein removal and hippuric acid excretion); (2) protein metabolic activities (serum albumin and globulin; NPN; urea

nitrogen; plasma amino acid nitrogen and uric acid nitrogen; and methionine utilization); (3) carbohydrate metabolism (glycogen storage test); (4) fat and steroid metabolism (serum free and esterified cholesterol; metabolism of administered androgen, as manifested by 17-ketosteroid excretion); (5) certain tests dependent upon aberrations of serum globulin and lipoglobulin (prothrombin time; cephalin cholesterol flocculation; thymol turbidity; and sedimentation rate). Only a few of these are emphasized in this phase of the study (*vide infra*).

Scheme of Evaluation. As clinical, histologic and chemical data accumulated we found it necessary to reduce our system to the simplest possible terms if we were to find any basis for correlation.

The textbook description of the liver is that of a great organ comprised of multiple, tiny functional units, these units being so designed that blood from the portal system, containing the products of intestinal digestion, is mixed with highly oxygenated blood from the hepatic artery just before its passage between the rows of hepatic cells in the anatomic lobule. During this passage, through the joint activity of the Kupffer cells and the liver cells, certain metabolites are removed from and others added to the stream which then rejoins the general circulation by way of the hepatic vein. The normal histologic structure and functions of such a lobule are shown schematically in Figure 1.

In arriving at a system of histologic evaluation, we initially searched for any abnormality or series of abnormalities in liver cells *per se* which would show consistent correlation with specific clinical or chemical findings. To date no such specific correlation has been found; hence we still find it necessary to speak of "gross hepatocellular change, as manifested by aberration in size and shape of liver cells, by widespread multinucleation, and by abnormal staining characteristics." Aside from such complex hepatocellular pathology, study of any considerable number of biopsy sections focuses one's attention upon the relative amount of

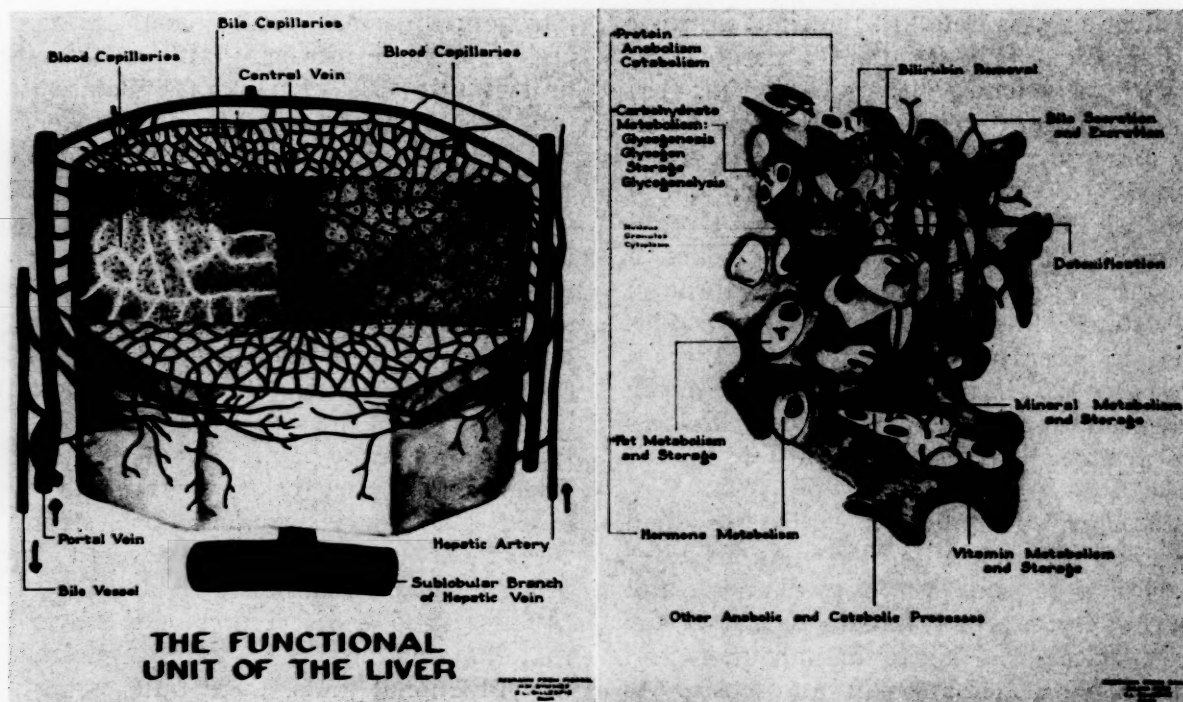


FIG. 1. Schematic presentation of structure and function of the hepatic lobule. (Courtesy of authors and publisher.)

connective tissue present and upon the amount and kind of cellular and non-cellular infiltrations found within and between lobules. Histologic evaluation of this sort followed by correlation of the biopsy sections with clinical and chemical findings resulted in the establishment of the following concept for evaluation and correlation:

$$\begin{array}{rcl} \text{Dietary} & & \text{Toxic Agent} \\ \text{Insufficiency} & + & (\text{Infectious or Chemical}) \\ & = & \text{Hepatocellular} + \text{Phagocytic} \\ & & \text{Damage} + \text{Infiltration} \end{array}$$

Enzymes or other agents produced by damaged liver cells and/or phagocytes result in fibroblastic proliferation.

Interpretation of liver sections, then, may be based upon the following criteria: (1) Cellular infiltration (round cells and other phagocytes) constitutes an index of activity, usually correlated with the cephalin cholesterol flocculation and other similar tests and at times with the serum bilirubin level. (2) Hepatocellular change, as manifested by aberration in size and shape of liver cells, by widespread multinucleation and by ab-

normal staining characteristics, is an index of activity and of extent and severity of the hepatotoxic process. Chemically, it is usually correlated with elevation of serum bilirubin, with bromsulfalein retention and with decreased hepatic glycogen storage. (3) Fibrosis is an index of duration and extent of over-all liver damage. It may be correlated with bromsulfalein and glycogen storage changes but in the presence of otherwise normal hepatic parenchyma may be compatible with normal chemistry.

The obvious defect in such an approach is its superficiality; its virtue lies in the avoidance of controversial material. That it represents only a transitional phase in the concept of the subject is apparent.

Laboratory Methods. All liver function tests and other chemical procedures have been performed by generally accepted and proven procedures.⁵⁻²¹ The Howe sodium sulfate precipitation has been used for globulin precipitation; it is recognized that this may at times give misleading information in patients with liver disease but other methods (electrophoresis excepted) are not yet adequately standardized. Bromsulfalein

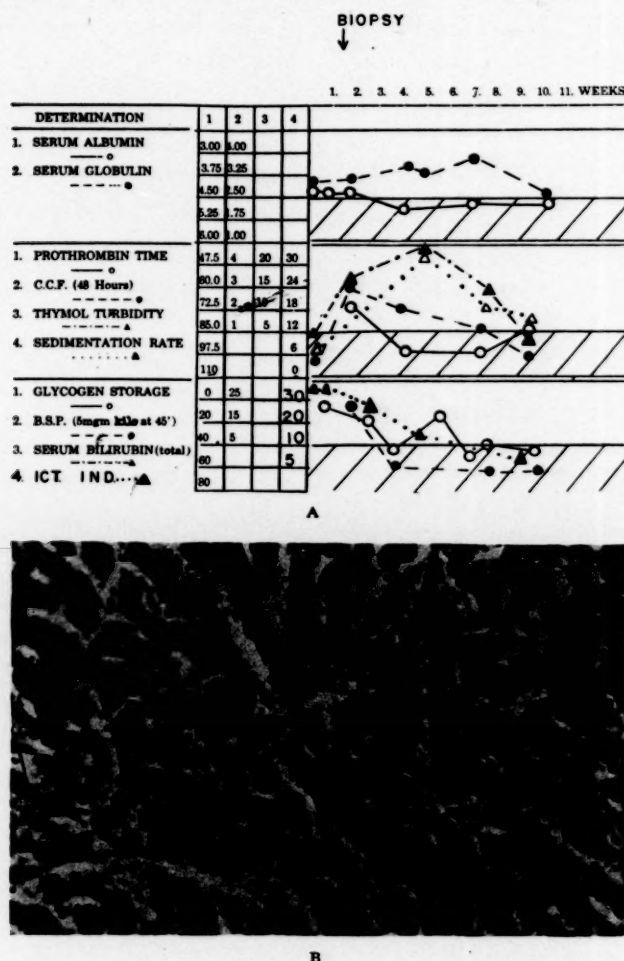


FIG. 2. Case 1. A and B, chemical and histologic findings; diagnosis: hepatitis, acute.

colorimetry was performed with the Beckman spectrophotometer.

FINDINGS

CASE 1. Acute Liver Damage. H. A. U., No. 153350, a male, aged thirty-two, had been ill for five weeks at the time of admission. The onset of his disease was quite typical of acute hepatitis, consisting of a history of malaise followed by the appearance of dark urine, nausea, vomiting, fever and clinical jaundice.

On admission his findings were: nutrition—fair; scleral icterus—3+; liver size—7 cm. in the anterior axillary line; splenomegaly—none; venous dilation—none; spider angiomas—none; ascites—none; dependent edema—none; gross vitamin deficiency—minimal; gynecomastia—none; appetite—poor; fetor hepaticus—none. He represented, then, a patient with a typical viral hepatitis of more than average severity,

showing at the time of admission no tendency to spontaneous resolution.

Biopsy obtained eight days after admission showed: (1) three plus round cell infiltration involving not only the periportal area but all peripheral portions of the lobule; (2) one plus increase in fibroblasts in the portal region; (3) widening of the bile capillaries; (4) the presence of bile thrombi; (5) abnormalities of size, shape and staining quality of the liver cells.

Chemical findings at the time of the initial biopsy included: cephalin cholesterol flocculation, sedimentation rate and prothrombin time—all abnormal immediately preceding the biopsy; thymol turbidity—normal, later becoming abnormal. Strangely enough, both sedimentation rate and cephalin cholesterol flocculation were normal on admission despite the five-week duration of the disease. For this we have no explanation. Hepatic glycogen storage

was markedly diminished; bromsulfalein removal, diminished; and icterus index, 3+ elevated.

EVALUATION:

1. Activity

Histology—marked cellular infiltration—hence marked activity

Chemistry—cephalin flocculation and sedimentation rates abnormal

Correlation—good

2. Extent and Duration

Histology—fibroblastic proliferation—not marked; hepatocellular change—marked

Chemistry—Bromsulfalein removal—diminished; glycogen storage—markedly diminished

INTERPRETATION:

Histology—widespread active process of recent onset

Chemistry—widespread active process, duration unknown

Correlation—good

This man was admitted at the same time as Case II (*vide infra*). Both were placed on a balance study regimen in which they received the equivalent of 115 Gm. of protein as casein hydrolysate intravenously in addition to other essential dietary constituents. On this program the patient improved clinically and chemically and his liver receded under the costal margin within two weeks so that a second section was not obtained. The rapid resolution under adequate therapy would suggest a relatively recent process and hence would make for even better correlation. The histologic and chemical findings are shown in Figure 2.

CASE II. J. O. N., No. 153359, a male, aged twenty, had been ill for three weeks at the time of admission. His past history was possibly of significance inasmuch as he had had an attack of jaundice some years previously and had recently had a chancre for which he had been treated with arsenic, bismuth and penicillin.

The onset of his present illness was classical for viral hepatitis. With the exception of a somewhat more intense icterus, higher fever and more marked hepatomegaly, his pertinent clinical findings on admission were identical with those in Case I. Their general clinical similarity and the severity of the disease process caused us to select them for a balance study which will be described elsewhere.

Liver biopsy was obtained immediately following admission and again seven weeks later. These biopsies showed: (1) intense round cell infiltration, less apparent in the seven-week biopsy but still definitely present; (2) fibrosis of sufficient degree to make the concept of pre-existing liver damage mandatory; (3) widening of bile capillaries; (4) the presence of bile thrombi; and (5) extreme alterations of normal hepatocellular structure, namely, abnormal staining characteristics, multinucleation and gross variation in cell architecture. The seven-week biopsy showed essential disappearance of (3), (4) and (5) but persistence of (1) and (2).

At the time of the first biopsy all tests were abnormal chemically with the exception of thymol turbidity. Seven weeks later (third biopsy) the bromsulfalein and glycogen storage tests had reverted to normal as had also the cephalin cholesterol flocculation. The sedimentation rate continued high although less so, and the thymol turbidity had become abnormal. The histologic and chemical findings are shown in Figure 3.

EVALUATION:

1. Activity

Histology—round cell infiltration throughout, as well as major hepatocellular abnormality

Chemistry—all tests initially abnormal; at the time of the seven-week biopsy the thymol turbidity test and the sedimentation rate were the only remaining abnormal chemical findings

Correlation—good, if one uses both cephalin cholesterol flocculation and thymol turbidity. The cephalin cholesterol flocculation alone would be misleading as an index of activity in late convalescence (*vide infra*)

2. Extent and Duration

Histology—initial, (B1) fibroblastic proliferation 2+, hepatocellular change 3+: final, (B2) fibroblastic proliferation 2+; hepatocellular change, nearly normal

Chemistry—bromsulfalein and glycogen storage, both initially abnormal, had reverted to normal limits at the time of the seven-week biopsy

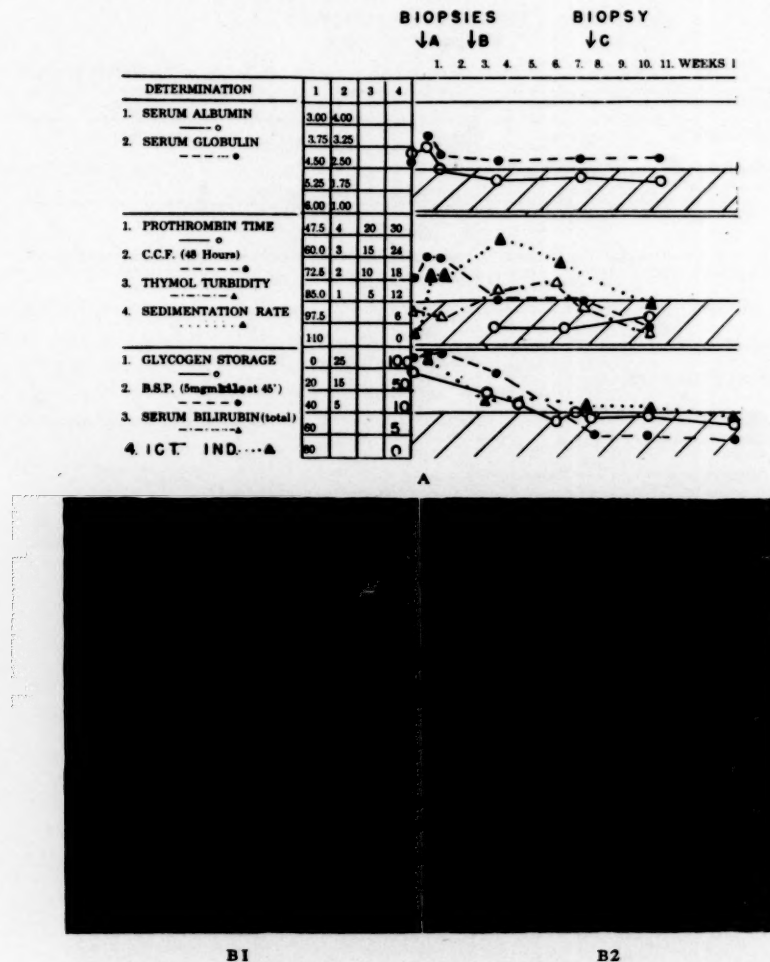


FIG. 3. Case II. A and B, chemical and histologic findings; diagnosis: hepatitis, acute; (B1) initial biopsy; (B2) final biopsy.

INTERPRETATION:

Histology—widespread severe, acute process, superimposed upon pre-existing liver damage

Chemistry—widespread, active process, duration unknown

Correlation—good

This man's further progress was satisfactory and he was subsequently discharged from the hospital clinically and chemically well but with a liver undoubtedly badly scarred and probably vulnerable to exposure to noxious agents.

CASE III. W. I. N., No. 153579, a male, aged twenty-six, was admitted with a history of a typical onset of acute viral hepatitis two months previously. He had been on a partial regimen of bed rest elsewhere before admission to this hospital. On admission here he still had moderate clinical icterus which had almost disappeared at the time of the first biopsy two weeks later.

Except for hepatomegaly, moderate anorexia and some weakness, he was free of symptoms and signs at the time of the first biopsy. At the time of the second biopsy three weeks later he showed steady clinical improvement and decreasing hepatomegaly.

The histologic findings were: initial, (B1) round cell infiltration 2+; hepatocellular changes, minimal; fibrosis 1+; three weeks later, (B2) almost normal liver architecture.

The chemical findings at the time of initial biopsy were: cephalin cholesterol flocculation, normal; thymol turbidity and sedimentation rate, moderately abnormal; bromsulfalein, normal; and glycogen storage, moderately decreased; at the time of second biopsy, all findings were normal except the glycogen storage test. The histological and chemical findings are shown in Figure 4.

As in Case II the best correlation in terms of acuteness is noted between the thymol turbidity

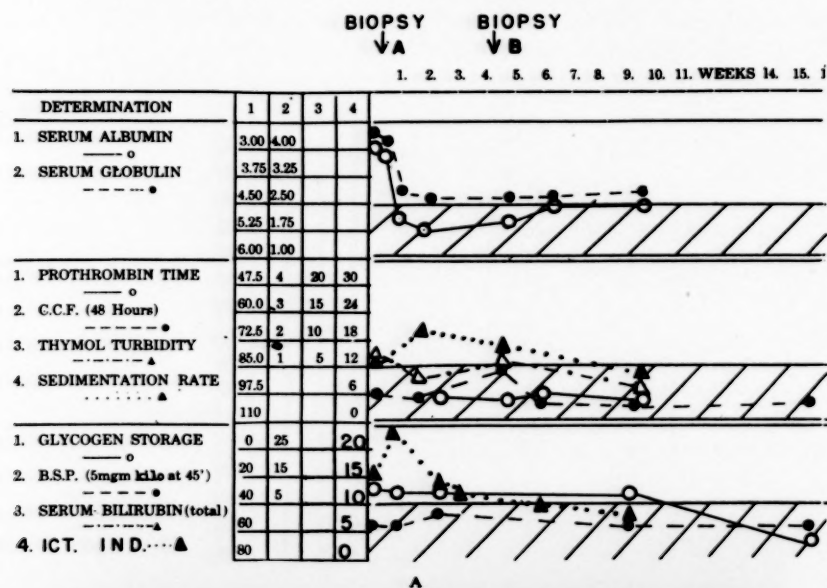


FIG. 4. Case III. A and B, chemical and histologic findings in patient W.I.N.; diagnosis: hepatitis, acute. (B1) initial biopsy; (B2) final biopsy.

and the round cell infiltration. The normal cephalin cholesterol flocculation is probably referable to the length of time elapsing since the onset of the disease.

The abnormal glycogen storage is not correlated with any demonstrable histologic abnormality in the second biopsy section. That this man had significant hepatomegaly long after all other liver function tests had become normal, and that his glycogen storage did eventually reach normal levels at about the time his hepatomegaly disappeared are of interest.

The general correlation was fair. His subsequent course was eventually that of thorough convalescence, namely, about seven months after the onset of the disease.

CASE IV. *Hepatitis, Chronic.* C. U. M., No. 149147, a male, aged twenty-six, was admitted for study approximately six months after the onset of an attack of acute hepatitis which had apparently been quite severe. Clinical jaundice was said to have persisted for four months. Spider angiomas appeared five weeks after the onset of the disease and were present throughout his period of observation in this hospital. He gave a history of jaundice ten years previously.

On admission, his findings were: general nutrition—fair-poor; scleral icterus—1+; liver size (AAL)—4 cm., quite hard; spleen—±; venous dilation—0; spider angiomas—2+; ascites—0; dependent edema—0; “B” deficiency—moderately red tongue; appetite—poor; gynecomastia—0; “fotor”—present.

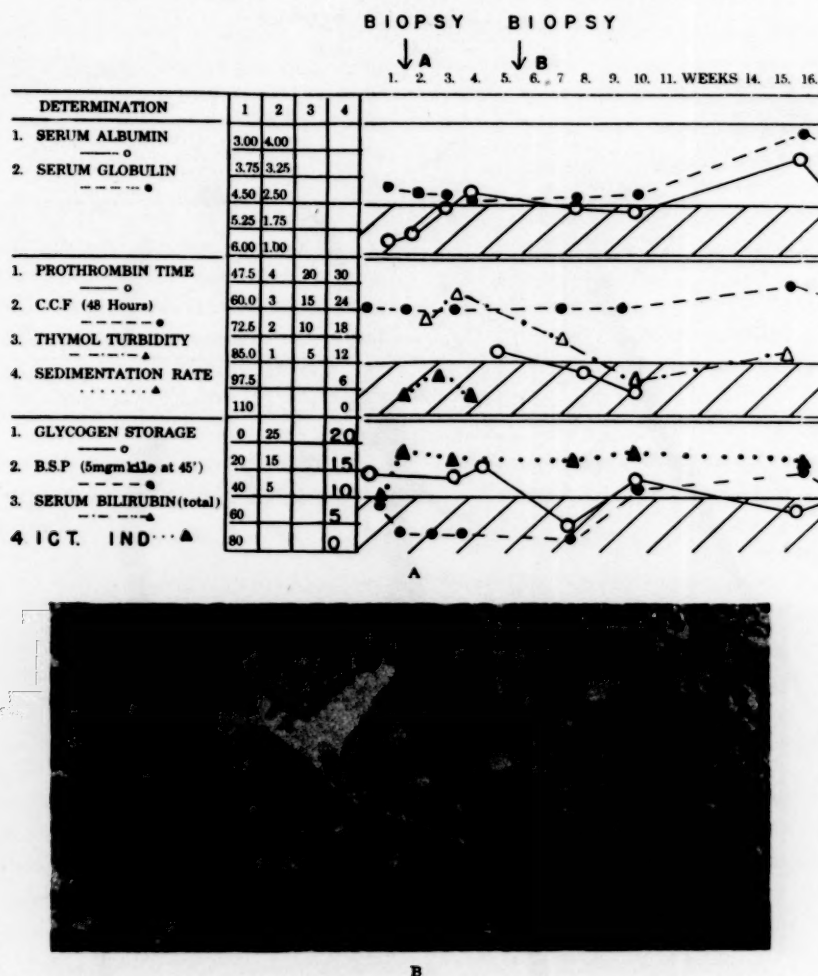


FIG. 5. Case IV. A and B, chemical and histologic findings in patient C.U.M.; diagnosis: hepatitis, chronic (viral).

Biopsy was performed on several occasions but was productive of only one good specimen, perhaps because of widespread fibrosis. The section shown was obtained just before the beginning of the chemical study. (Fig. 5.) The findings were (1) cellular infiltration, 1+; (2) fibrosis, 1+; and (3) hepatocellular abnormality, 2+.

The chemical findings were: cephalin cholesterol flocculation, abnormal throughout; thymol turbidity, abnormal during most of study; sedimentation rate, normal; glycogen storage, decreased; bromsulfalein, normal at time of biopsy, intermittently abnormal thereafter, over many months.

INTERPRETATION:

Histology—hepatocellular abnormality was the most striking feature in the section obtained; it is highly probable that this man has a much greater degree of gen-

eralized replacement fibrosis than is shown in this section, however

Chemistry—the continued abnormality of the cephalin cholesterol flocculation and glycogen storage are compatible with a concept of continued activity and with a process which is widespread in its involvement

Correlation—fair, in spite of the lack of much cellular infiltration; continuing low grade hepatocellular damage from some toxin, insufficient at this state to excite a marked phagocytic response would appear to be a reasonable explanation

Progress—at this writing, eight months after admission and fourteen months after the onset of this disease, he is still abnormal clinically, chemically and histologically, despite rest, diet and lipotropic agents

Chronic Liver Damage. Five patients are presented under this heading. These five

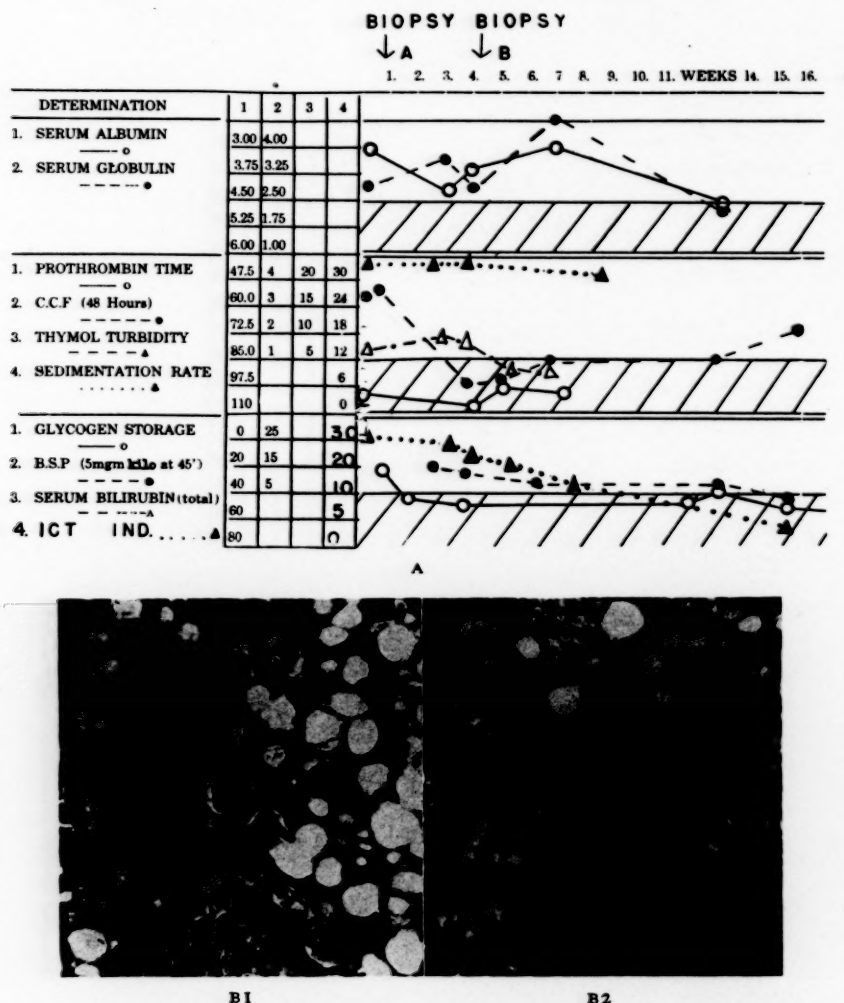


FIG. 6. Case V. A and B, chemical and histologic findings in patient B.E.A.; diagnosis: "cirrhosis"; (B1) initial biopsy; (B2) final biopsy.

are perhaps "representative" of the entire group of "cirrhotics" who have come to us for study and treatment. All five have one factor in common—chronic alcoholism. All have been "spree drinkers" and hence have undoubtedly had periods of significant dietary insufficiency. All had ascites on admission. All but one on "adequate" therapy lost his ascites in a relatively short period of time. All but one has been or will be discharged in reasonably good clinical condition.

CASE V. B. E. A., No. S47-509, forty-three year old, heavy set male, was admitted in near coma, deeply jaundiced, dyspneic and edematous. Aside from his alcoholism extending over a twenty-year period, he has had rheumatic fever with cardiac damage, a previous attack of

jaundice fourteen years ago and lues in 1936 treated with arsenic and bismuth. Acute alcoholism probably precipitated his present episode.

Examination showed: general nutrition—fair; scleral icterus—3+; liver size (AAL)—12 cm., hard; spleen—just palpable; venous dilation—plus 1; spider angiomas—1+; ascites—plus 1; dependent edema—2+; "B" deficiency 2+; appetite—very poor on admission; gynecomastia—none; fetor—present.

Biopsy was performed the day following admission (B1) and again twenty-six days later, (B2) at which time his liver extended only 2 to 3 cm. below the rib margin and he was clinically symptom-free. Therapy during this period had consisted of high protein intake, digitalis and lipotropic agents. Histologic and chemical findings are shown in Figure 6.

The histological evaluation initially, in line with the proposed scheme for evaluation, was: (1) round cell infiltration—3+, hence marked activity; (2) fibrosis—3+, hence widespread, pre-existing damage; (3) hepatocellular change—3+, hence a widespread, active lesion; (4) fatty infiltration—3+; in view of the variety of physiologic processes which can produce this picture, its significance is by no means clear (*vide infra*). Finally, the rapid reversion toward the normal in less than four weeks was most striking. Only fibrosis, slight phagocytic cell and moderate fatty infiltration remained.

Chemically the picture was that of abnormality of all liver function tests studied, all reverting to normal in the space of three weeks. Correlation was excellent.

The rate of improvement in this man must represent a liver still possessing marked regenerative capacity, despite the histologic evidence of widespread fibrosis. The patient was discharged essentially clinically and chemically well about four and one-half months after admission. We understand that he died some weeks later in acute congestive failure in the course of another alcoholic debauch.

The last four men to be described have more factors in common than at variance. To avoid tiresome repetition, we shall present a composite picture of the four and then stress the factors of fundamental importance to this study in which they differ.

The common factors were: (1) age—all but one (W. R. I.—aged thirty-five) were between forty and fifty years of age; (2) alcoholism of more than fifteen years' duration; (3) ascites—present in all on admission; all but one (D. R. E.) had lost his ascites on standard therapy prior to the beginning of this study; (4) hepatomegaly—moderate to marked.

CASE VI. D. R. E., No. 139977. A clinical description of this man must with any propriety include a brief mention of his personal characteristics. We found him over a period of eighteen months to be everything an ex-chronic alcoholic should not be—lovable, dependable, a booster to the morale of the entire ward.

On entry he possessed a huge bulging belly which, superimposed on his long, gangling frame, produced a somewhat Puckish impression. At one time or another he received every

therapeutic agent which has been proven or suspected to be of value in cirrhosis, with little effect. During the last five months of his life (he finally died from a ruptured esophageal varix) he probably received more serum albumin than anyone in history. Despite its failure to do more than delay the inevitable, we count each cubic centimeter well spent. He is described in considerable detail in a paper dealing with protein balance studies. Since he was our first biopsy patient and has just left us as this paper nears completion, we wish to erect a small verbal monument to a friend.

The clinical findings, in addition to those already described, showed splenomegaly—2+; peripheral varicosities—3+; dependent edema—1-3+; fetor—3+ and spiders—3+.

His liver edge and surface were grossly irregular, hard and retracted from the abdominal wall, making biopsy difficult and potentially hazardous. One biopsy was obtained three months before the intensive chemical study was begun. A later biopsy attempt was unsuccessful. The histologic and chemical findings are shown in Figure 7.

The histologic section was obtained three months before the intensive chemical study was begun. On the basis of autopsy findings it is undoubtedly representative of the patient's hepatic histology at any time during the study. The findings were: (1) round cell infiltration—3+, hence marked activity; (2) fibrosis—4+, hence long duration and widespread involvement; (3) hepatocellular change—3+, hence generalized, active involvement.

At no time in the chemical study was any liver function test, except the prothrombin time, even close to normal. The histochemical correlation then, in our crude sense, may be said to be excellent.

CASE VII. D. A. N., No. 15447. Together with the other two men still to be described, this patient is representative of patients with severe liver disease, progressing over many years but still reversible, at least to a degree compatible with fairly normal activity.

Clinically, he showed every textbook finding of advanced cirrhosis, including considerable splenomegaly. Two months after admission he was free of ascites and dependent edema. On his departure some months later, precipitated (against advice) by domestic difficulties, he was clinically vastly improved with almost no remaining hepatomegaly although chemically

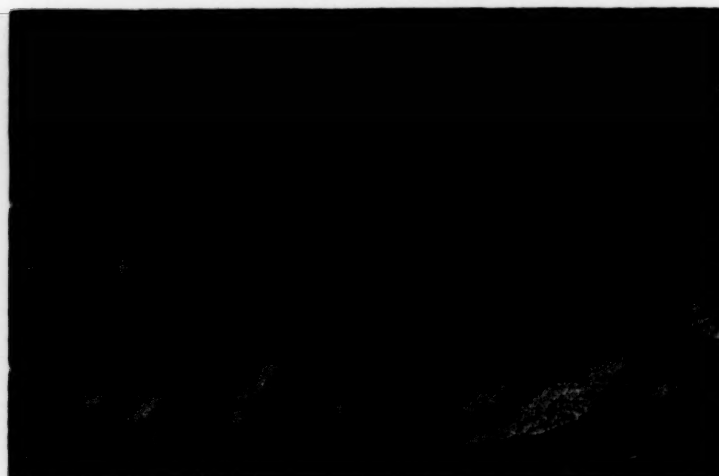
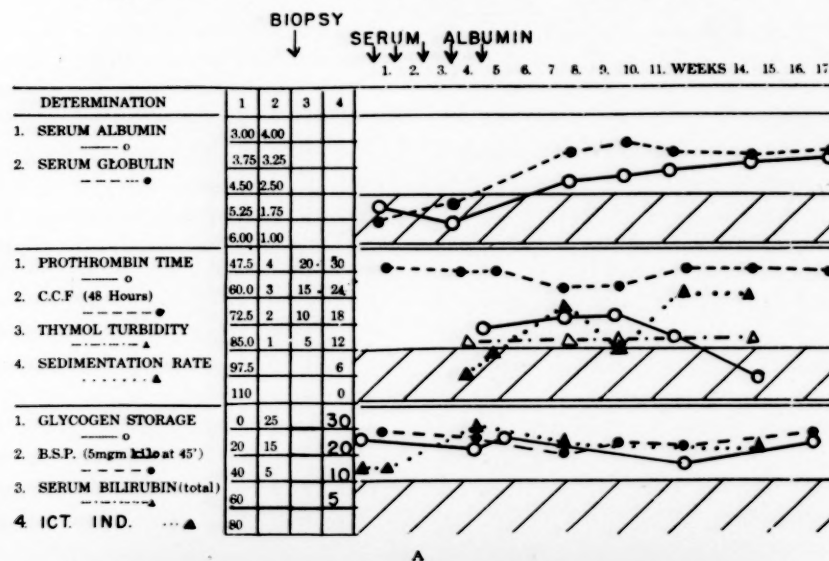


FIG. 7. Case VI. A and B, chemical and histologic findings in patient D.R.E.; diagnosis: "cirrhosis."

still far from well. His letters inform us that he has steered completely clear of alcohol and is doing a full days' work with no difficulty. The histologic and chemical findings are shown in Figure 8.

Biopsies obtained early in the study (but after the disappearance of ascites) (B1) and again a month later (B2) showed little change. Activity: Moderate phagocytic cell infiltration; considerable hepatocellular change. The tremendous amount of fibrosis with choking off of tiny islands of distorted liver cells speak for the widespread damage of long duration.

At no time during the four-month period of intensive chemical study were any normal liver function tests noted, either those which are related to activity or those which are indicative

of widespread damage although the glycogen storage test became less abnormal.

We do not know what the prognosis in terms of life expectancy may be in this man. He is returning to us in the near future for a brief check of his chemical panel. If the findings have reverted to normal his outlook should be good, if he still shows evidence of continued activity, our prognostic outlook will veer in a pessimistic direction. If he has reverted to normal on a program of full activity, we shall question the soundness of the concept of the need for prolonged bed rest in convalescent but not quiescent "cirrhotics."*

CASE VIII. P. A. R., No. 151189, a male, in

* Chemical re-evaluation nine months after discharge showed improvement in all tests.

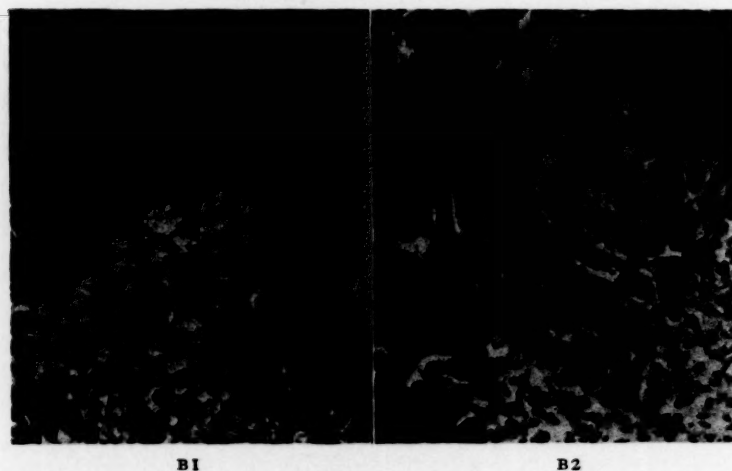
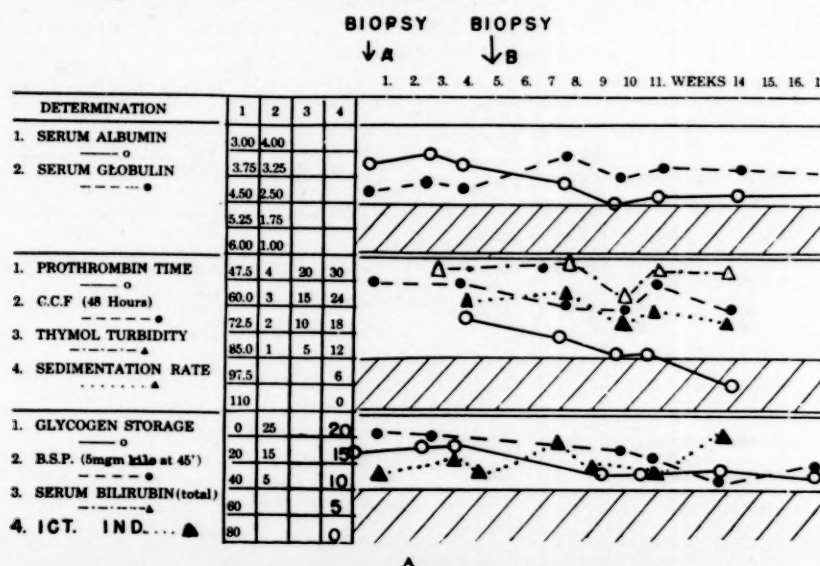


FIG. 8. Case VII. A and B, chemical and histologic findings in patient D.A.N.; diagnosis: "cirrhosis"; (B1) and (B2) are biopsies one month apart.

addition to chronic ethanol addiction had lues some twenty odd years previously and was treated with fairly large amounts of arsenic and heavy metals without incident. His general clinical status was essentially identical on admission with that of Case VII. His chemical response to therapy was even better than that of D. A. N., despite occasional alcohol imbibition. The histologic and chemical findings are shown in Figure 9.

Widespread fibrosis was apparent in both sections. The second section, obtained six to seven weeks after the first during which time impressive clinical improvement had occurred, showed less phagocytic cell infiltration and more normal appearing liver cells. The evaluation was: widespread chronic liver damage (fibrosis)

and decreasing activity of the hepatotoxic process.

The continued abnormality of all liver function tests for a four-month period followed by a gradual decline of the bromsulfalein and glycogen storage test toward normal is the most impressive part of the picture. Resumption of alcohol abuse occurred in the latter part of the study for a considerable time; this may have accounted for the continued abnormality of the cephalin cholesterol flocculation test.

The interpretation was an hepatotoxic process, widespread in extent, but of decreasing intensity; correlation (histology and chemistry) fair. The histology fails to account for the continued abnormal cephalin cholesterol flocculation.

CASE IX. W. R. I., No. 150443, a male, is

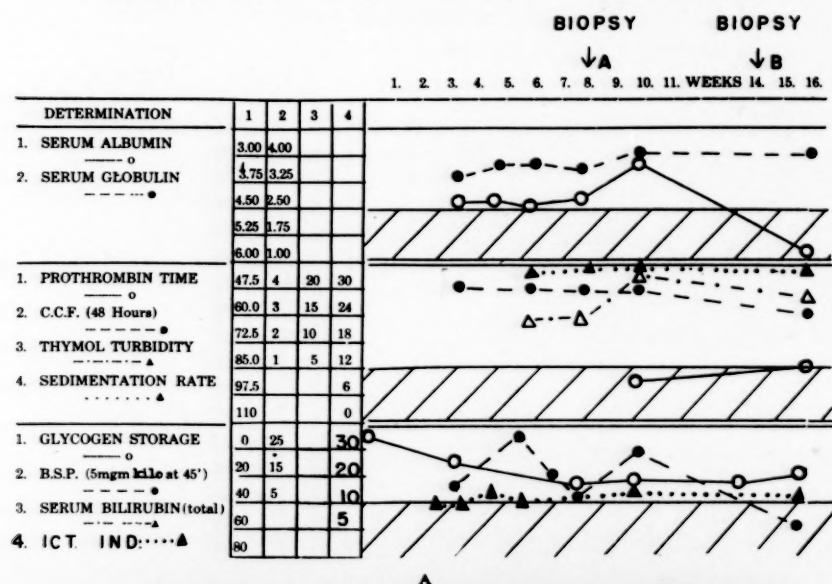


FIG. 9. Case VIII. A and B, histologic and chemical findings in patient P.A.R.: diagnosis: "cirrhosis"; (B1) and (B2) are biopsies six weeks apart.

noteworthy only in that, in contrast to the majority of patients studied, he showed complete lack of correlation between histology and chemistry. Clinically, he was the youngest of all cirrhotics included in this report (thirty-five years), showed the best nutrition, and minimal ascites. The histologic and chemical findings are shown in Figure 10.

Histologically, there was marked fibrosis, round cell infiltration, some in connective tissue, but not in parenchyma and slight hepatocellular change. The impression was that of moderate activity in the presence of widespread liver damage of prolonged duration.

There were normal findings throughout chemically except for transient decrease in glyco-

gen storage following an alcoholic debauch. Obviously the chemical findings would be compatible with the concept of a normal liver. Correlation was very bad; for this we have no explanation at the present time.

This man became quite normal clinically in the space of two to three months. Even the alcoholic episode (which occurred while he was on leave) did not cause his liver to become palpable again.

Consideration of hepatic structure and function, together or singly, could extend interminably. We shall confine ourselves to a few comments on certain points raised by this work.

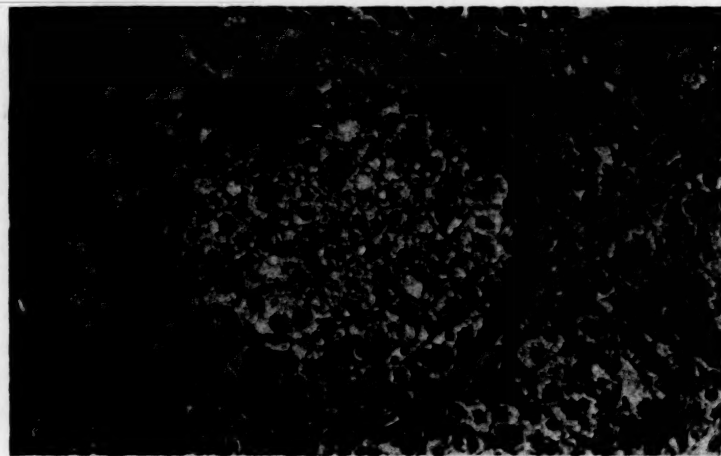
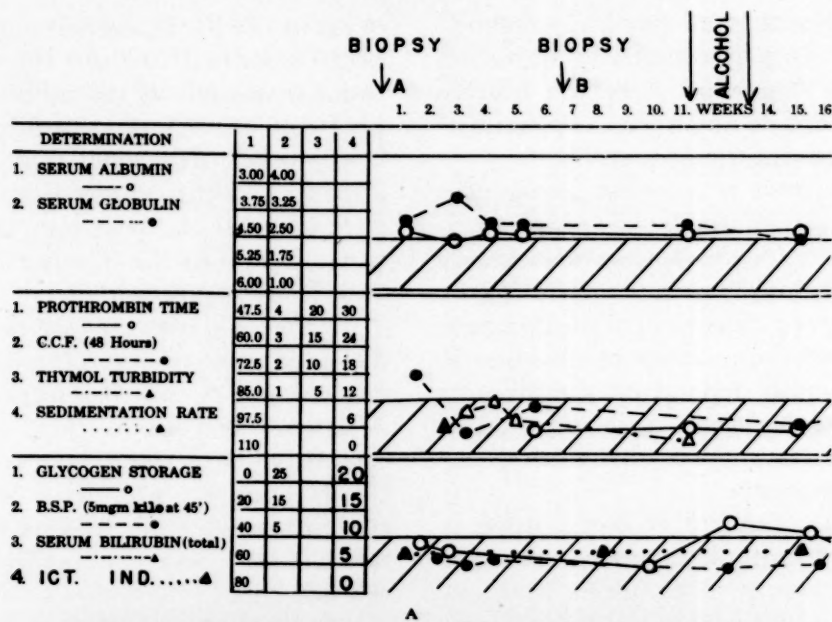


FIG. 10. Case IX. A and B, chemical and histologic findings in patient W.R.I.; diagnosis: "cirrhosis."

CLASSIFICATION OF HEPATIC DISEASE

Chronic Liver Damage. Retention of the term "cirrhosis" in any evaluation of the pathology or physiology of the liver would seem to have little to recommend it. Laennec first used the term in 1826 to describe the color of the liver in autopsy specimens characterized by extensive fibrosis and distortion.²² The later addition to medical nomenclature of the term "hypertrophic biliary cirrhosis" to identify an alleged entity supposedly separate and distinct from Laennec's "atrophic portal cirrhosis" has served only to confuse genera-

tions of medical students and practitioners. It would seem to us probable that many concepts of the pathogenesis, pathology and pathologic physiology of liver disease will rise and fall before the final correct answer emerges.

As one step in this evolutionary process the following may be in order: (1) complete and permanent abandonment of the term "cirrhosis" except in a historical sense; (2) complete abandonment of the concept of "portal" and "biliary" forms of liver disease in the time-honored sense; fibrosis, "biliary obstruction" and hepatocellular

damage are present in all cases; (3) reclassification on a simple, essentially unitarian basis, perhaps somewhat after the fashion previously noted; in any event, a classification which includes the concept of:

A toxin, endogenous or exogenous, acting upon hepatic cells made vulnerable by specific nutritional deficiency resulting in hepatocellular damage with consequent fibrosis of greater or lesser degree.

The rapidity of progression of the damage, its duration and the amount of fibroblastic proliferation would depend on the amount and nature of the toxin and the extent, duration and nature of the underlying nutritional deficiency.

The foregoing concept is based upon a rather vast amount of experimental data originating in many laboratories and extending back over a period of fifteen years, and upon the observations of Patek in 1937 and 1941^{23,24} and of Connor in 1939²⁵ relating to the role of nutritional deficiency in the production of human liver damage. Essentially this concept has formed the basis for the rather remarkably successful therapy now in use in the treatment of patients with liver disease.

Acute Hepatitis. The term "acute hepatitis" is probably both accurate and desirable. Just how variations in the nature of the toxic agent may determine differences in the type of inflammatory reaction, and hence differences in the ultimate histologic picture in the liver, still remains to be shown. Moon adequately summarizes the literature in this field.²⁶ Also to be demonstrated is the role of preceding nutritional deficiency in the production of hepatitis.

Perhaps the final logical nomenclature of liver disease will consist of acute, chronic and healed hepatitis with a modifying adjective referable to the specific etiologic agent.

Fatty Liver. In a previous paper²⁷ we have summarized some of the evidence in the literature relative to the production of fatty livers and of "cirrhotic" livers in animals by dietary means.

Of the patients whom we have presented in this series only one had a significant amount

of fat in the liver parenchyma. Had biopsies been obtained before the institution of therapy in some of the other men it is quite probable that fatty infiltration would have been found. However that may be, it is apparent in this group that severe hepatic parenchymal damage can be present and can progress in the absence of any demonstrable fat deposition.

Conversely, we do not believe that the disappearance of liver fat concurrently with clinical and chemical improvement in such a patient as Case v (Fig. 6) of necessity establishes any significant relationship between liver fat and liver damage. Work currently underway in a number of laboratories may help to further clarify this relationship.

LIVER FUNCTION

The search for better tests of liver function still continues in many laboratories and clinics. For purposes of correlation with structural alteration we have placed the greatest stress on the cephalin-cholesterol flocculation, the bromsulfalein removal, the serum bilirubin and measurement of hepatic glycogen storage.²⁸ This choice is perhaps open to criticism. The inclusion of the thymol turbidity test is probably desirable. It can be said, however, that statistically all four tests show an impressive correlation with the clinical and histologic course of acute and chronic liver disease. That complete lack of correlation with the clinical or histologic findings can occur is well represented in Case ix. (Fig. 10.)

ROLE OF LIVER BIOPSY

In our opinion, the role of liver biopsy may be summarized in a very few words: (1) As a research tool it is justified and valuable. A vast amount of work remains to be done in the evaluation of specific hepatocellular changes. It can serve (2) as a diagnostic tool, when clinical, chemical and roentgenologic findings still leave one in doubt; this applies particularly in the differential diagnosis between non-specific liver damage and tumor. The inability to

be sure that the section obtained is representative of the entire organ is an obvious and serious limitation of the procedure. Moreover, a blind approach to a highly vascular, bile secreting, intraperitoneal organ can never be devoid of risk.

SUMMARY

From study of liver biopsy sections and chemical liver function tests one can only hope for present purposes to obtain rather gross information as to the *activity* of the process which has resulted or is resulting in liver damage, and information as to the *extent and duration* of the process.

Activity is correlated histologically with phagocytic cell infiltration and with hepatocellular change as manifested by widespread multinucleation, abnormalities of cell shape and size, and abnormalities of staining characteristics. The chemical abnormalities which indicate activity are the cephalin cholesterol flocculation and thymol turbidity tests as well as elevation of the serum bilirubin and/or icterus index.

Extent and duration of the hepatotoxic process are manifested histologically by hepatocellular change and by fibrosis. The chemical changes which are found in liver damage of widespread extent and/or long duration are abnormal bromsulphalein retention, diminished hepatic glycogen storage and elevation of the serum bilirubin and/or icterus index.

It is to be emphasized that the above observations are extremely superficial and have nothing to recommend them but their simplicity.

From the foregoing it is evident that our knowledge of liver histology and physiology is in need of many additions; and that when such additional knowledge is obtained, revision of the present archaic classification of liver disease will be in order. An approach to such a reclassification is presented.

Acknowledgment is made to Wyeth, Inc., for supplies of methionine used in the conduct of this work; to Mead Johnson & Co., for supplies of Amigen; and to Eli Lilly & Co. for alpha-tocopherol.

Acknowledgment is made also to Mrs. M. F. Jack for her able assistance in the editing and typing of this and other papers from this laboratory.

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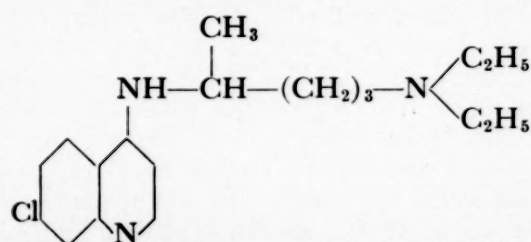
The Treatment of Hepatic Amebiasis with Chloroquine*

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THE wartime antimalarial drug research program disclosed a number of highly active compounds of the 4-amino-quinoline series. It seemed logical to determine whether their antiplasmodial activity extended to other pathogenic protozoa. The infection selected for study was that with *Endameba histolytica* because of its relative prevalence among protozoal infections in the New York area. Furthermore, although the value of iodo-hydroxy-quinoline derivatives in the management of intestinal amebiasis had been well established, it had not been determined whether iodine was an essential substituent of the quinoline nucleus for antiamebic activity.

Of the various 4-amino-quinoline derivatives tested for antimalarial activity the greatest amount of information was available concerning chloroquine,^{1,2} 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline, which had proven one of the more active and less toxic members of the series.



Chloroquine. 7-chloro-4(4-diethylamino-1-methylbutylamino) quinoline

Certain pharmacologic characteristics of this compound made it appear a priori that amebic infections of the liver rather than of the colon would be the test object of

choice. These properties of chloroquine include: (1) its extensive localization in the liver (some five hundred times its plasma concentration) occurring in many animal species and presumably man,² (2) a three- to fourfold lesser degree of localization

TABLE I
AMEBACIDAL ACTIVITY OF VARIOUS DRUGS IN VITRO
AGAINST TROPHOZOITES OF *E. HISTOLYTICA*

Drug	Dilutions of Drugs				Medium
	1/500	1/2000	1/10,000	1/50,000	
Emetine	0 0	0 0	0 0	+ 0	Egg Liver
Chloroquine	0 0	0 0	+ 0	+ 0	Egg Liver
Carbarsone	0 0	+ 0	+ +	+ +	Egg Liver
Anayodin	0 0	± ±	+ +	+ +	Egg Liver

+ = Growth.
0 = No growth.

within the intestinal walls,³ and (3) its almost complete absorption from the gastrointestinal tract,² only some 8 per cent of the daily dose being excreted in the feces, so that the contents of the intestinal lumen, especially the colon, contain a rather small drug concentration.

In vitro studies with trophozoites of *Endameba histolytica* (Table I) conducted by Dr. Harold W. Brown revealed that chloroquine has amebacidal activity supe-

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rior to that of anayodin and carbarsone but less than that of emetine. Employing a different strain of *E. histolytica*, Dennis⁴ found comparable *in vitro* antiamebic activity of chloroquine. It must be emphasized, however, that extrapolation of *in*

TABLE II
RESULTS OF CHLOROQUINE TREATMENT OF AMEBIASIS

	No. Treated	No. Cured
Intestinal.....	32	17
Hepatic.....	22	22

vitro results to therapeutic activity in human disease may be wholly fallacious. Dennis was unable to demonstrate any activity of chloroquine against natural *Endameba criceti* infections in hamsters.

RESULTS

A preliminary publication⁵ has indicated that chloroquine does possess antiamebic activity in human infections of the liver and colon. So far as intestinal amebiasis is concerned, chloroquine alone has effected symptomatic and parasitologic cure in seventeen of thirty-two cases with follow-up periods of from two to twenty-four months. In regard to hepatic amebiasis the author has now studied seven patients with amebic hepatitis, each of whom was successfully treated with chloroquine. Shookhoff⁶ has confirmed these results in a series of twelve cases of amebic hepatitis. Sodeman⁷ has had comparable results in two cases of acute amebic hepatitis. Murgatroyd^{8,9} has reported the cure of a draining amebic abscess of the liver with chloroquine. Thus twenty-two patients with hepatic amebiasis have now been cured with chloroquine.

The purpose of this publication is to present detailed information concerning the author's seven cases and of Murgatroyd's case which is most informative.

PLAN OF TREATMENT

Oral dosage regimens for testing chloroquine in human amebiasis were devised

with the idea of administering close to the minimal toxic dosage for a period of two to three weeks in order to allow the drug the maximum opportunity for demonstrating *in vivo* antiamebic activity; this resulted in giving, in most instances, a priming or loading dose of 0.6 Gm. of the base for two days in order to saturate the tissues. Plasma and tissue concentrations were then maintained by continuing with a dose of 0.3 Gm. of the base daily for two to three weeks.* Determinations of plasma drug concentrations were not performed in the present study but earlier observations² indicate that they would approximate 176 micrograms per liter.

CASE REPORTS

CASE 1. P. H., No. 845126. A fifty-eight-year old white male who had been in China between 1943 and 1945 entered the Presbyterian Hospital in October, 1946. During the eleven weeks prior to admission he had been bothered by two to five loose stools a day associated with crampy, low abdominal pains before and during defecation. He entered the hospital not for this but for an eye operation, following which he developed chills and fever to 104°F. with enlargement and tenderness of the liver accompanied by a leukocytosis of 20,000. X-ray revealed elevation of the right diaphragm and a small right pleural effusion. The cephalin-cholesterol flocculation test was negative. Following demonstration of *Endameba histolytica* in the feces the patient was treated with emetine parenterally, 60 mg. a day for a total of 780 mg., and with chiniofon orally, 3.0 Gm. a day to a total dose of 60.0 Gm. This regimen produced a favorable but only partial effect in that, after a month of treatment, although no amebas could be found in the feces, the patient still had a low grade fever up to 101°F., anorexia, nausea and enlargement and tenderness of the liver. At this

* While the dose of chloroquine has been expressed in terms of the base or active chemical agent, the salt actually used in this study was the diphosphate; 0.15 Gm. of chloroquine base is contained in 0.25 Gm. of chloroquine diphosphate. In terms of the salt then, the dosage schedule employed is 1.0 Gm. of chloroquine diphosphate daily for two days, followed by 0.5 Gm. of chloroquine diphosphate daily for two to three weeks. Chloroquine diphosphate is sold under the name of Aralen diphosphate (Winthrop-Stearns Inc.).

point chloroquine was administered in doses of 0.3 Gm. of the base for thirty-one days. Within a week all symptoms disappeared, the appetite improved followed by a gain in weight and the liver became neither obviously enlarged nor tender. It must be mentioned that during the first week of treatment the patient complained of nausea about one hour after each dose of chloroquine. The nausea, however, disappeared despite continued medication. The patient has remained well for the succeeding twenty-four months.

CASE II. P. H. 852316. A sixty-one-year old male came to the Presbyterian Hospital from El Salvador in December, 1946, complaining of "colitis" of ten years' duration manifested by upper abdominal cramps and two to three loose stools a day, a continuous dull pain in the right upper quadrant of eight months' duration, and for the past six months weakness, anorexia and weight loss. Physical examination revealed a tender liver, which was enlarged to two to three finger-breadths below the right costal margin, and left lower quadrant tenderness. Complete blood count, urinalysis and Kline test were normal. The cephalin-cholesterol flocculation test was negative. Serum alkaline phosphatase was 3.3 Bodansky units per cent (B. U. per cent). At thirty minutes there was 15 per cent bromsulfalein (BSP) retention. Cysts and trophozoites of *Endameba histolytica* were found in the stools. Barium enema revealed evidence of inflammation in the descending and sigmoid colon. A gastrointestinal series was interpreted as showing gastroduodenitis. The cholecystogram was normal. Chloroquine was administered in doses of 0.6 Gm. of the base daily for two days followed by 0.3 Gm. of the base daily for twelve days. On the second day of treatment neither enlargement nor tenderness of the liver could be demonstrated. On the last day of treatment anorexia, nausea and vomiting occurred. This was thought to be due perhaps to the gastroduodenitis rather than to chloroquine since all symptoms promptly cleared following administration of alkali. After treatment four stools were negative for amebas, the BSP test showed only 7 per cent retention and all symptoms had disappeared. The follow-up period is only one and one-half months because at this time the patient returned to El Salvador and has not been heard from since.

CASE III. P. H. No. 862925. A fifty-three-year old white male who had never left the

United States entered the Presbyterian Hospital in March, 1947. The previous medical history included an appendectomy in 1909, typhoid fever in 1911, an undiagnosed illness in 1943 quite similar to the present illness, and a duodenal ulcer with symptoms in 1944 but not since then. Abdominal cramps, diarrhea and constipation were denied. The present illness was of two to three weeks' duration and consisted of persistent high fever, occasional shaking chills, a constant severe epigastric and right upper quadrant pain which radiated to the right shoulder, and a 5 pound weight loss. Physical examination revealed fever, right upper quadrant tenderness and muscle spasm as well as right costovertebral angle percussion tenderness. The white blood count was 17,200, erythrocyte sedimentation rate (ESR) was 122 mm. at one hour, BSP retention at thirty minutes was 12 per cent, and the serum alkaline phosphatase was elevated to 8.2 B.U. per cent. The cephalin-cholesterol flocculation test was negative. The hemoglobin concentration, red blood count, urinalysis, stool culture, various bacterial agglutination tests and the Kline test were normal. Gastrointestinal series revealed a duodenal ulcer. Barium enema showed a deformed contracted cecum, a patent ileocecal valve and a loop of terminal ileum adherent to the cecum. Fluoroscopy demonstrated splinting of the right diaphragm and a small pleural effusion. Cholecystogram was normal. Trophozoites of *Endameba histolytica* were found in the stools and the amebiasis complement fixation test was positive (+++). At the end of the second hospital week, fever and pain had abated somewhat but were still present, as were the diaphragmatic splinting, pleural effusion, ESR of 116 mm. at one hour, elevated phosphatase and the BSP retention. Chloroquine was then given in doses of 0.6 Gm. of the base daily for two days, followed by 0.3 Gm. of the base for nineteen days. (Fig. 1.) On the fourth day of treatment all pain, tenderness and fever had disappeared as had the diaphragmatic splinting and pleural effusion. As treatment continued the ESR fell progressively to 11, the BSP from 12 per cent to 0 per cent retention and the alkaline phosphatase from 8.2 to 4.4 B.U. per cent. The patient regained his appetite, weight and strength. During the third week of chloroquine treatment the stools, which had become negative, again showed amebas which promptly disappeared with administration of chiniofon, 2.25 Gm.

daily for eleven days. The patient has been well for the succeeding twenty-one months during which purged stools every two months have revealed no amebas, the complement fixation test has decreased from +++ to \pm , and the barium enema reveals marked improvement in the cecum.

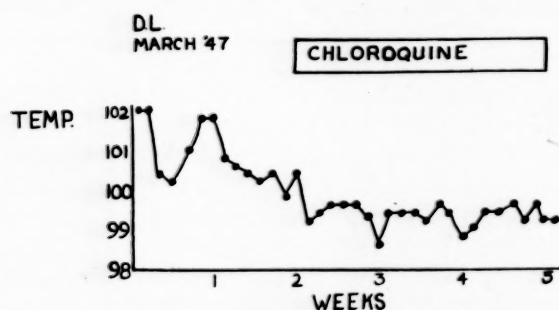


FIG. 1. Temperature chart in Case III. In this and subsequent charts only the maximal daily temperatures are recorded.

CASE IV. V. H., No. 97395. A twenty-five-year old colored male veteran was admitted to the Veterans Administration Hospital in the Bronx in July, 1947, complaining of chills, fever, right upper quadrant pain, cough, anorexia and nausea of four days' duration. During the previous seven months several episodes of nausea had occurred accompanied by abdominal cramps and diarrhea which occasionally had been bloody. The only point of importance in the past history was a thirteen-week hospitalization period with acute infectious hepatitis while in the Philippines. Physical examination revealed fever and an enlarged, tender liver with considerable overlying muscle spasm. Laboratory studies were as follows: blood count normal including a negative test for sickling, urinalysis negative, cephalin-cholesterol flocculation test negative, serum albumin 3.6 Gm. per cent, globulin 2.5 Gm. per cent, alkaline phosphatase 1.6 B.U. per cent and an icterus index of 8. There was 5 per cent retention of BSP at forty-five minutes. Purged stools showed many trophozoites of *Endameba histolytica*. Various bacterial agglutination tests and blood cultures were negative. The amebiasis complement fixation test was + + + +. X-ray of the lungs was normal. Barium enema demonstrated considerable inflammation of the terminal ileum, cecum and ascending colon. For three and one-half weeks the patient received treatment (Fig. 2) for intestinal amebiasis consisting of 2.53 Gm. of diodoquin orally for ten days followed by

1.0 Gm. of carbarsone a day for ten days, the latter being concurrent with retention enemas containing 8.8 Gm. per cent chiniofon for seven nights. This eliminated parasites from the feces but had no effect upon the hepatitis. At the end of this treatment the liver was still tender and enlarged to 6 cm. below the right costal

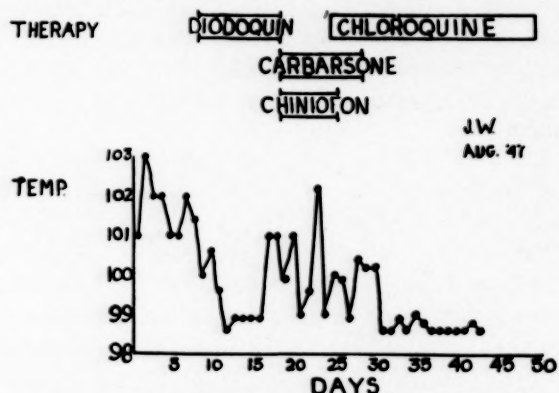


FIG. 2. Temperature chart in Case IV.

margin, a right-sided pleurisy had developed as manifested by pleuritic pain and friction rub accompanied by radiologic evidence of a small pleural effusion. In addition the phosphatase had risen from 1.6 to 6.0 B.U. per cent and the white blood count from 8,400 to 18,000. At this juncture chloroquine was administered in doses of 0.6 Gm. of the base daily for two days followed by 0.3 Gm. of the base daily for nineteen days. On the fourth day of this therapy the liver was only 3 cm. below the costal margin and was much less tender with no overlying muscle spasm. At the same time the white count had dropped from 18,000 to 7,500. On the eighth day of chloroquine treatment the liver was neither palpable nor tender, the phosphatase had dropped from 6.0 to 2.6 B.U. and BSP from 6 per cent retention to no retention in forty-five minutes, the patient had regained his appetite and some of his lost weight and the pleurisy had cleared completely. He has been perfectly well now for fourteen months.

CASE V. P. H., No. 894190. A twenty-six-year old male veteran entered Presbyterian Hospital in December, 1947, complaining of two months of fever up to 104°F. with night sweats and 30 pounds weight loss, as well as three weeks of right upper quadrant pain which radiated to the right shoulder. The whole illness began in November, 1942, in the midwest before the patient ever left the United States. The symptoms then were anorexia and nausea. Two

months later weekly bouts of diarrhea and right lower quadrant pains began for which an appendectomy was performed in April, 1943, without relief of the symptoms which continued intermittently. Early in 1944 a duodenal ulcer was demonstrated by a gastrointestinal x-ray but there was only slight relief on an ulcer diet. Bloody diarrhea first appeared in May, 1944, at which time the patient was hospitalized for six months in an army general hospital where he was told he had colitis, was treated with emetine and discharged from the army in November, 1944. Between this time and November, 1947 the patient suffered from several episodes of cramps and diarrhea. On November 4, 1947, the sudden onset of fever occurred which ranged from 102° to 104°F., chilliness, sweats, anorexia and profound malaise for which the patient received 5,000,000 units of penicillin over a six-day period with a diagnosis of pneumonia. Following this treatment there were two weeks with no symptoms after which the fever and nausea recurred but were now complicated by severe right upper quadrant pain radiating to the back and shoulder. Throughout these two months there were no cramps or diarrhea.

Physical examination disclosed fever of 102°F., splinting of the right diaphragm and a tender liver which extended three finger-breadths below the costal margin. Blood count revealed leukocytosis of 14,000 with a moderate neutrophilia and a slightly low hemoglobin of 12.5 Gm. per cent. The ESR was 60 mm. at one hour. Urinalysis was negative. Eleven stool examinations, most of which followed purges, failed to reveal *Endameba histolytica* or any other parasite. The stool guaiac test was repeatedly negative as were stool cultures for pathogenic bacteria. Several blood cultures showed no growth. Blood chemical determinations revealed alkaline phosphatase 3.5 B.U. per cent, urea nitrogen 16 mg. per cent, trace of bilirubin, albumin 4.6 Gm. per cent, globulin 2.8 Gm. per cent and euglobulin 0.6 Gm. per cent. There was 70 per cent retention of BSP in thirty minutes. The cephalin-cholesterol flocculation and the thymol turbidity tests were negative. Various x-ray and fluoroscopic examinations showed normal heart and lungs, marked splinting of the right diaphragm, a duodenal ulcer, a tender irritable and deformed cecum and a constant area of spasm in the hepatic flexure. A cholecystogram and intra-

venous pyelogram were normal. The amebiasis complement fixation test was ++.

After admission the patient received 4,000,000 units of penicillin daily for 17 days without effect upon fever or pain. The temperature which had been 102°F. on admission fell to 100°F. and remained there for a week at which time it spiked over a three-day period to 103.6°F. Chloroquine was then administered in doses of 0.6 Gm. of the base for two days followed by 0.3 Gm. of the base for nineteen days. By the third day of this treatment there was no fever and the liver which had been extremely tender and enlarged to two finger-breadths below the costal margin gradually decreased in tenderness and size and after a week was normal to percussion and palpation. The white blood count dropped from 15,900 to 7,200; the ESR from 31 to 2 mm.; the BSP from 20 per cent retention to none.

About one week after discontinuation of chloroquine the patient developed a crampy pain which began in the right upper quadrant and passed to the left upper quadrant which was relieved by defecation. This was accompanied by a rise in temperature to 100° to 101°F. Despite the pain and fever there was neither enlargement nor tenderness of the liver. Because of the presence of a duodenal ulcer an ulcer diet was prescribed but gave no relief. In view of this and because the white blood count, sedimentation rate and liver function tests remained normal and since the barium enema again revealed inflammatory changes in the cecum and hepatic flexure, it was decided that this episode might be due to amebic colitis. Accordingly, the patient was placed on diodoquin in doses of 1.89 Gm. daily for three weeks and an additional course of chloroquine. Under this regimen there was prompt and permanent alleviation of the fever and crampy pains. The patient gained 15 pounds in weight in the succeeding ten months during which he has been asymptomatic and his liver normal to physical and chemical examination. The amebiasis complement fixation test which initially was ++ is now ±.

CASE VI. M. H., No. 59087. A twenty year old American-born white housewife who had not traveled outside the general metropolitan New York area was admitted to the Methodist Hospital, Brooklyn, in May, 1948, and again in June, 1948, for treatment of amebiasis.

Previous history included an appendectomy

at the age of sixteen. The present illness began following a normal delivery in December, 1947. It consisted of fatigue, anorexia, 11 pound weight loss, fever, headaches and abdominal cramps associated with up to fifteen watery, mucoid and occasionally bloody stools a day.

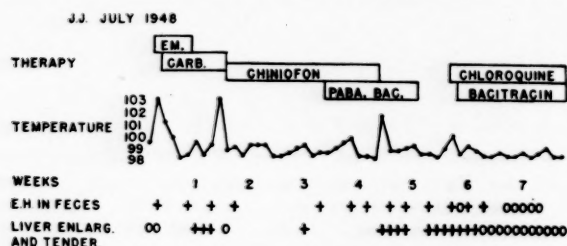


FIG. 3. Chart in Case VI.

The episodes of diarrhea lasted from three days to two weeks and occurred four times between December, 1947, and May, 1948. At this time physical examination revealed generalized abdominal tenderness and proctoscopy showed a bleeding granular mucosa. Stool examination revealed trophozoites and cysts of *Endameba histolytica*. The blood count was not remarkable except for a 14 per cent eosinophilia. X-ray of the chest was negative. During the first admission the patient received emetine subcutaneously, 60 mg. daily for eight days, and was started upon diodoquin 1.89 Gm. daily for seventeen days. After emetine therapy was completed she was discharged from the hospital to continue the diodoquin at home. While still on this drug, she again developed nausea, cramps and bloody diarrhea because of which she was readmitted. At this time a very tender mass in the right lower quadrant had developed. Amebas were still present in the feces and the complement fixation test for amebiasis was positive. The white blood count ranged from 6,000 to 15,000 with a persistent eosinophilia of from 11 to 30 per cent. The cephalin-cholesterol flocculation test was negative on the first occasion, positive later and finally negative. The thymol turbidity test was negative. The serum albumin was 3.1 Gm. per cent and the globulin 3.0 Gm. per cent. The serum alkaline phosphatase was 3.4 B.U. per cent. Serum agglutination tests were negative for typhoid O and H, paratyphoid A and B, *Brucella abortus* and *Proteus* X19. Urinalyses were normal in respect to specific gravity, protein, reducing substances and microscopic examination with the exception of microscopic hematuria on two occasions while sulfonamides were being administered. Stool

cultures failed to grow out pathogenic enteric bacteria.

Because of chills, fever, the tender abdominal mass and stools containing gross blood and pus, the patient (Fig. 3) was given during the first week 2.5 million units of penicillin, 10.5 Gm. of streptomycin, and 38 Gm. of sulfadiazine, along with 300 mg. of emetine and 6.5 Gm. carbarson. Despite this on the seventh day the patient developed right upper quadrant pain associated with a tender liver which extended three finger-breadths below the costal margin while amebas persisted in the feces. On the tenth hospital day following the intravenous administration of parenamine, a pyrogenic reaction occurred followed by a thrombophlebitis in the left arm at the injection site. The next antiamebic drug to be used was chiniofon in daily doses of 0.75 Gm. for nineteen days, during the last seven days of which paraaminobenzoic acid¹⁰ was also administered in doses of 5.5 Gm. daily. Then bacitracin, which is currently under investigation as an intestinal amebicide,^{11,12} was administered by mouth in doses of 40,000 units daily for five days. Despite these drugs the liver remained enlarged and tender, the right lower quadrant mass was still present, bloody diarrhea persisted and *Endameba histolytica* was still found in the feces. At this time chloroquine in daily doses of 0.3 Gm. of the base was given for fourteen days. On the second day of chloroquine treatment the liver was less enlarged and much less tender, and after the fourth day of therapy it was neither palpable nor tender. Following the improvement in the hepatitis under chloroquine, oral bacitracin was re-administered in larger doses, 80,000 units daily for thirteen days. Under the combined therapy the stools became negative for *Endameba histolytica* and the right lower quadrant mass gradually disappeared. The patient regained and maintained good health during the succeeding five months during which repeated stool examinations have been negative.

In connection with the eosinophilia, there was no history of allergies or trichinosis nor were ova or larvae of helminths demonstrated in the stools. Five months later the white blood count was 6,450 with only 4 per cent eosinophilia.

CASE VII. P. H., No. 922146. A forty-six-year old white native of Argentina was admitted to the Presbyterian Hospital in September, 1948, complaining of chills, fever and sweats of three days' duration. He had "colitis" of

many years' duration, manifested by episodes of diarrhea which was occasionally bloody. Three months prior to admission *Endameba histolytica* had been demonstrated in his feces following which he received injections of emetine and strychnine. No oral amebacidal treat-

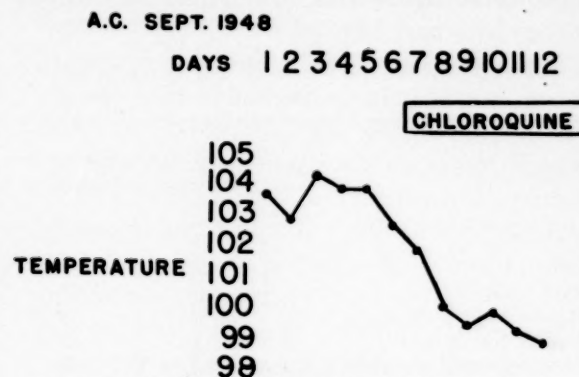


FIG. 4. Temperature chart in Case VII.

ment was administered. The present illness began on an airplane en route to New York. At the time of admission, physical examination revealed an acutely ill, febrile male exhibiting marked diaphoresis but with no localizing signs. On the third hospital day epigastric pain occurred along with an enlarged and tender left lobe of the liver. Laboratory tests revealed a leukocytosis of 17,000 with 86 per cent neutrophils, normal urinalysis, ESR of 74 mm., no malaria parasites, negative blood and stool cultures, negative Kline test, negative agglutination tests against typhoid, paratyphoid, *Brucella abortus* and *Proteus* X19 organisms. The cephalin-cholesterol flocculation and thymol turbidity tests were negative. Serum alkaline phosphatase was 2.8 B.U. per cent and the serum bilirubin less than 0.5 mg. per cent. X-ray of the chest was negative except for evidence of strip atelectasis at the left base. Stool examination revealed cysts of *Endameba histolytica*. The amebiasis complement fixation test was anticomplementary initially and later positive.

Following admission (Fig. 4) fever and sweats persisted, and the left lobe of the liver became enlarged, tender and painful. Penicillin was administered beginning the second hospital day in doses of one half to one million units a day without effect. On the sixth hospital day chloroquine was administered in doses of 0.6 Gm. of the base for two days followed by 0.3 Gm. of the base daily. One and one-half days after the drug was started the temperature became normal

MARCH, 1949



FIG. 5. Draining amebic abscess of the liver, Case VIII.

and the enlargement and tenderness of the liver gradually disappeared. After one week of chloroquine therapy the patient was discharged from the hospital, remained asymptomatic for one more week at which time he left the country.

CASE VIII. The patient was admitted to the Hospital for Tropical Diseases in London* with a discharging amebic abscess of the liver (Fig. 5) which had been opened surgically more than four months before and which had failed to heal despite intensive treatment, including several courses of emetine, as well as penicillin and streptomycin for various secondary infections that had supervened. Both the stools and the liver pus consistently revealed numerous trophozoites of *Endameba histolytica*. Because of the history of resistance to treatment the effects of various therapeutic agents were observed. Emetine was administered by various routes for nineteen days. (Fig. 6.) Emetine hydrochloride was injected subcutaneously for ten days in doses of 60 mg. daily for the first five days and then 90 mg. daily for the second five days. Emetine bismuthous iodide, 120 mg. a day, was given orally during the second five days. From the tenth to the nineteenth day a 0.012 per cent solution of emetine hydrochloride in physiologic saline was administered by continuous irrigation of the abscess cavity. In addition 1 million units of penicillin were given intramuscularly a day for the first five days.

* The data of this case were graciously supplied by Dr. F. Murgatroyd and Dr. N. H. Fairley of London.

Also given during the second five days were irrigations of the abscess cavity twice daily with 40 ml. of 0.1 per cent proflavine.

Under this regimen parasites disappeared from the feces but to support this aspect of the therapy diodoquin was administered orally in

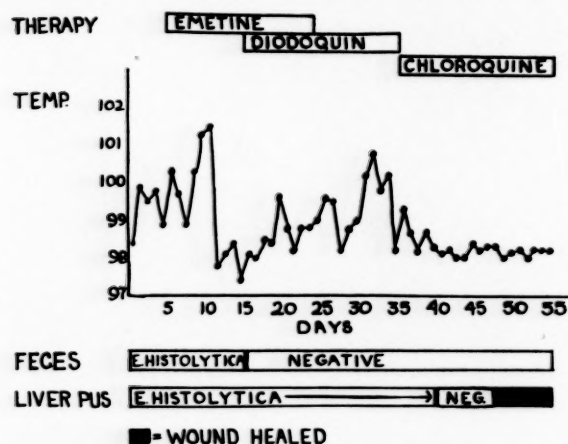


FIG. 6. Chart in Case VIII.

doses of 2.4 Gm. daily for twenty-one days. Despite all this amebas persisted in the pus discharging from the liver abscess. At this point administration of chloroquine was started in doses of 0.75 Gm. daily for eighteen days. Fever promptly disappeared. From the fifth day of chloroquine treatment amebas could no longer be found in the liver pus. By the twelfth day the discharge had ceased and the wound was healed. Two weeks following treatment the patient was discharged from the hospital and was prescribed a maintenance dose of 0.25 Gm. of chloroquine biweekly for three months. Two months after discharge from the hospital the patient continued to be in good health, was asymptomatic, had gained seventeen pounds, the wound was soundly healed, there was neither tenderness nor obvious enlargement of the liver, no amebas were found in the stool and the blood count was normal.

COMMENTS

It is recognized that there are perils in establishing a diagnosis without isolation of the etiologic agent from the organ involved. Because it did not seem justified, liver biopsy in the suspected presence of *Endameba histolytica* was not performed. The presence of amebas in the feces does not necessarily imply their presence within

an inflamed liver and, conversely, their absence from the feces does not necessarily imply their absence from an inflamed liver. Hence, in all but one case reliance has been placed upon the prompt disappearance of symptoms, signs and abnormal laboratory

TABLE III
SUMMARY OF PERTINENT SIGNS AND LABORATORY TESTS

	Present or Positive	Absent or Negative
Chills.....	7	1
Fever over 102°F.....	7	1
Hepatic enlargement.....	8	0
Hepatic tenderness.....	8	0
Diaphragmatic pleurisy.....	4	3
Icterus.....	0	8
<i>E. histolytica</i> in feces.....	7	1
<i>E. histolytica</i> in liver pus.....	1	
Amebiasis complement fixation test.....	5	
Cephalin-flocculation test.....	1	6
Bromsulfalein retention.....	4	
Elevated alkaline phosphatase.....	2	4

tests indicative of hepatitis following drug administration. Table III summarizes the objective evidence that these patients had hepatitis as well as amebiasis. The fact that the hepatitis in each instance began to clear within one to two days and progressively improved without recurrence is the critical element in establishing the activity of chloroquine against hepatic amebiasis. Needless to say, none of the patients had active malaria. Chloroquine has been administered without apparent benefit or detriment in the presence of acute infectious hepatitis.¹³ The only other hepatic disease known to be affected by chloroquine is infection with *Clonorchis sinensis*¹³ which was not present in any of the patients reported. Furthermore, in these patients no agent which is known to infect the liver other than *Endameba histolytica* was demonstrated. It consequently appears that the salutary effects observed in these patients may properly be ascribed to the effect of chloroquine upon infection of the liver with *Endameba histolytica*.

For the treatment of extra-intestinal amebiasis, the commonest lesion of which is found in the liver as diffuse inflammation with or without abscess formation, emetine is highly effective and may serve as a standard of reference for compounds with similar activity. So far as the patients who received chloroquine alone are concerned, the response to medication seemed just as prompt and as complete as would have been expected had emetine been used. Cases I, VI and VIII afford a comparison between chloroquine and emetine. It will be noted that even in this small series emetine is not uniformly effective in the treatment of amebic hepatitis or amebic abscess of the liver. The fact that chloroquine administered subsequent to the inadequate response to emetine was in each instance successful is significant, but is not to be taken as a prediction that the antiamebic activity of chloroquine will subsequently prove always to be superior to that of emetine.

It may well be possible to revise downward the daily dose and/or the duration of treatment with chloroquine for amebic hepatitis. With so few cases for study this was not attempted other than to vary the duration from two to four weeks and to omit the priming dose in two instances. On the other hand, upward revision of the daily dose and/or duration of treatment, if tolerated, might yield superior results in amebic colitis.

Toxicity of Chloroquine. Chloroquine causes only minor toxic manifestations. With antimalarial doses (1.2 to 1.5 Gm. of the base over one to three days) the following symptoms are infrequently observed: mild and transient headache, disturbance of visual accommodation, pruritus and gastrointestinal complaints.^{1,2,14} Chronic toxicity studies^{2,15,16} in humans have not disclosed any serious toxic symptoms or signs. Chloroquine in the dosage schedule employed in the treatment of amebiasis, namely, 0.6 Gm. of the base daily for two days, followed by 0.3 Gm. of the base daily for an additional twelve or nineteen days, has been administered to

forty patients, three of whom complained of nausea, one of transient pruritus and one of disturbed ocular accommodation. In no instance was the complaint of any magnitude and it was never necessary to interrupt or discontinue medication. Another patient reported by Most¹⁷ received concurrently chloroquine, emetine and diodoquin and developed generalized pruritus followed by mild epithelial desquamation, both of which began and terminated within one week. It might be significant that because of the combination of chloroquine and diodoquin, considerably more quinoline was being administered than if either had been used alone.

It is not the purpose of this paper to discuss the toxicity of emetine other than to mention that it does occur in the form of nausea, vomiting and diarrhea, and occasionally in the form of severe myositis and myocarditis. Chloroquine presents no such serious toxic potentialities and in addition does not require parenteral administration.

Correlation of Drug Localization with Activity. A disparity between the results obtained with various antiamebic agents, depending upon the location of the infection, has long been known to exist. Emetine has typified one fashion of activity in that it is highly effective in extra-intestinal amebiasis whereas when used alone it succeeds in eliminating permanently the ameba in only 10 to 15 per cent of cases of colitis.¹⁸ The iodohydroxyquinolines, on the other hand, are said to be effective in 70 to 90 per cent of intestinal infections but are without effect in extra-intestinal infections.

One explanation offered for this dichotomy of action has assumed a differential *in vivo* activity of these compounds against trophozoites and cysts. This concept, however, is based upon a fundamental misunderstanding of the pathogenesis of amebiasis. Amebic infection (Fig. 7) is established in the colon following the ingestion of cysts by their excystment into trophozoites which then invade the colonic mucosa. Following this either cysts or trophozoites may appear in the feces. Thus the form of

Endameba histolytica which is responsible for the initiation and perpetuation of colonic or metastatic infection is the trophozoite, and it is this which must be eradicated in order to cure the infection. Were the differential elimination of cysts in the colon

PATHOGENESIS OF HUMAN AMEBIASIS

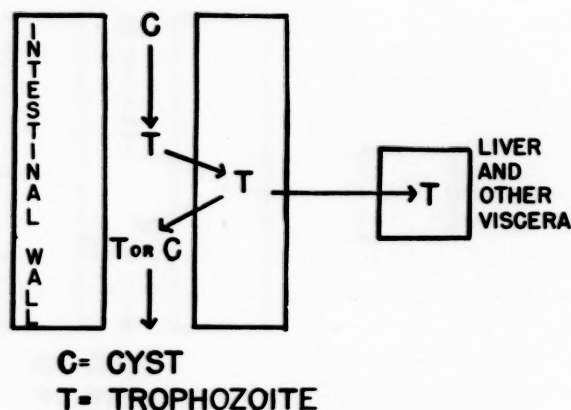


FIG. 7. A schematic drawing of amebic infection.

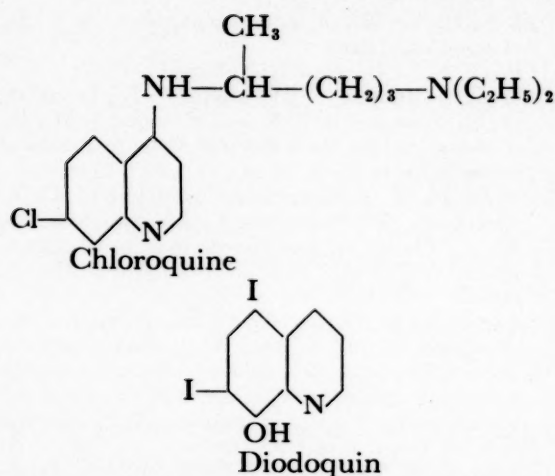
possible the trophozoites and hence persistent infection would remain. Hence the significance of the cyst in the feces is that its presence is not of importance to the disease of the host in whom it is only diagnostic of trophozoites activity within the colon, but is of importance as a means of infecting another host.

A more rational hypothesis may be constructed upon the degree of drug localization within infected tissues. One of the basic premises of this study was that if chloroquine had any *in vivo* antiamebic activity, it would be most apparent against amebas in the liver because of the high drug localization in that organ, and less apparent against amebas in the intestine because of the lesser degree of localization there. That the clinical results follow this pattern does not establish the point but it is of correlative interest that the recently published information of Parmer¹⁹ and Smith et al.²⁰ concerning the tissue distribution of emetine indicate that it parallels that of chloroquine in regard to the intestinal wall, liver and

other organs. Also in accord with this hypothesis is the efficacy of the iodohydroxyquinolines in intestinal amebiasis as opposed to their ineffectiveness against extraintestinal amebiasis. This can be correlated with the very small degree of absorption and consequently high intestinal concentration of these compounds which has been reported by Albright, Tabern and Gordon²¹ in regard to chiniofon.

Chance et al.²² have noted that in proportional doses a greater hepatic and intestinal localization of arsenic with trivalent arsine oxides occurs than with pentavalent arsonic acids to which class belong carbarsone, acetarsone, treparsol, etc. Such information may explain why carbarsone, a rather efficient intestinal amebicide, has proven ineffective in extra-intestinal amebiasis. Anderson et al.²³ have found that certain arsine oxides, such as carbarsone oxide (the trivalent analog of carbarsone) and its dithiocarboxymethyl and dithiocarboxyphenyl derivatives possess amebicidal activity *in vitro* and in macaques greater than that of carbarsone. In animals the thioarsenites, as anticipated, were less toxic than their parent compound. Subsequently Anderson et al.²⁴ have successfully treated three patients with amebic hepatitis with thioarsenites. This is of considerable pharmacologic interest because it indicates that, like 4-aminoquinolines, arsenic can be delivered to the liver in therapeutic concentrations.

Presumably because of the lethal effect of iodine upon cysts of *Endameba histolytica* *in vitro*, the activity of the iodohydroxyquinolines upon trophozoites in human infections has been attributed to their iodine content. One compound is recommended because it contains twice as much iodine as others yet paradoxically is given in nearly twice the dosage of similar compounds with less iodine. A comparison of the formula of chloroquine, which contains no iodine, with that of diodoquin as a representative of the iodohydroxyquinolines reveals the quinoline nucleus as a common denominator.



This suggests that the quinoline nucleus or some metabolic degradation product thereof, rather than the iodine content, may represent the active amebicidal component in these compounds.

If the effects of amebicidal drugs are truly correlated with their localization in sufficient concentrations within selected tissues, the idea may be entertained that a single quinoline derivative may be found which can be administered in non-toxic dosage with the achievement of adequate amebicidal concentration within the intestine as well as the liver and other viscera which may be involved in amebiasis.

Role of Chloroquine in the Treatment of Amebiasis. Because it is clinically impossible to determine with accuracy in every case of intestinal amebiasis whether or not extra-intestinal involvement has occurred, and because of the high frequency of such metastatic infection observed in pathologic material,¹⁸ it is at least theoretically highly desirable to treat every patient with intestinal amebiasis with agents designed to eradicate amebae wherever they may be in the body. Until now emetine has been the only available agent for extra-intestinal amebiasis whereas there are several fairly efficient intestinal amebicides. The toxicity of emetine and the measures designed to minimize or prevent such toxicity have precluded the widespread practical application of the above principle. Since the lack of toxicity of chloroquine permits treatment

of even ambulatory patients, it is recommended that chloroquine be employed in addition to a more efficient intestinal amebicide for the treatment of all cases of intestinal amebiasis. Conversely, for the treatment of hepatic amebiasis, even in the absence of signs or symptoms of intestinal involvement, it is recommended that an intestinal amebicide be employed in addition to chloroquine in order to be more certain to eradicate any colonic focus of infection, because chloroquine is only about 50 per cent curative for intestinal amebiasis. Case v illustrates this point.

Because of the widespread use of chloroquine in the suppression of malaria, it would be profitable to determine whether this compound possesses any antiamebic suppressive or prophylactic properties.

CONCLUSION

Chloroquine is a safe and effective chemotherapeutic agent for the treatment of amebic infections of the liver, being at least as effective as emetine but without the toxicity of emetine. The combination of chloroquine with a superior intestinal antiamebic drug should permit adequate treatment of any amebic infection, and should permit wider use of antiamebic chemotherapy as a diagnostic and therapeutic test in obscure infections of the liver and intestine.

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For the privilege of studying and treating their patients, the author is deeply indebted to the following: Drs. F. K. Heath, A. R. Lamb, Sr., and G. C. Hennig of the Presbyterian Hospital, Dr. C. M. Guest of the Veterans Administration Hospital, Bronx, and Dr. J. A. Head of the Methodist Hospital, Brooklyn.

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Liver Function during Infectious Mononucleosis*

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DURING the course of infectious mononucleosis manifestations of involvement of various organs have been observed.¹⁻¹¹ The few postmortem examinations which have been made revealed the presence of widespread abnormalities.^{12,13,14} Evidence of hepatitis was demonstrated in each of these studies, and by biopsy in others.¹⁵⁻¹⁸ Jaundice was observed during infectious mononucleosis over twenty years ago and subsequently in occasional cases.^{19,20,21} Investigation of its pathogenesis has been made only recently.

Several series of cases of infectious mononucleosis have now been reported in which tests of liver function revealed abnormalities in a significant proportion.^{9,22-25} The results are, in general, similar to those obtained during infectious hepatitis.²⁶ Many cases of infectious mononucleosis resemble those with infectious hepatitis of virus etiology and the differentiation by either clinical or laboratory means is often difficult.^{26,27}

Since the etiology of the condition is not established, accurate specific criteria for its diagnosis are not available. It has been shown that the clinical features are so variable that the absence of the typical syndrome does not exclude the disease.^{2,3,9,10} It is fair to state that the diagnosis of infectious mononucleosis in the individual case at present must be presumptive and based upon clinical manifestations supported²⁸ by information supplied by nonspecific laboratory tests. Several virus infections provide features commonly associated with

infectious mononucleosis. German measles and, as indicated, infectious hepatitis are among the most difficult to differentiate. The evidence suggests that infectious mononucleosis is a specific infectious disease entity, but the possibility exists that the various manifestations are part of a syndrome which may be caused by one of several etiologic agents. Accurate evaluation of the significance of changes in liver function during infectious mononucleosis will require extended observation of patients after recovery and further correlation by clinical, biopsy and postmortem examinations.

It is the purpose of this report to present the results obtained by observation and liver function tests made during the study of a series of eighty-three cases in which the diagnosis of infectious mononucleosis was made.

METHODS

Liver function tests were performed during the course of infectious mononucleosis in eighty-three cases which were observed in the Department of Student Health of the University of Wisconsin from August, 1946, to June, 1948. All patients were between seventeen and thirty-four years of age. Fifty-five were men. All but two were hospitalized for varying periods. For the purpose of this study the diagnosis of infectious mononucleosis was made if the clinical features were clearly suggestive and either an increased lymphocyte percentage of the white blood cell differential count, with the appearance of abnormal forms, was present in the peripheral blood or a rise in heterophile anti-

* From the Departments of Medicine and Preventive Medicine and Student Health, University of Wisconsin Medical School, Madison, Wis. Supported in part by the Research Grants Division of the U.S. Public Health Service.

bodies to a titer of 1:128 or above occurred in the serum. Heterophile antibodies were not demonstrated in the serum of fifteen of the patients included. In eight of these the test was made only once, in each instance before the tenth or after the twentieth day. Four additional patients had a maximum titer of 1:64. The presence of other characteristic features seemed to justify the inclusion of these nineteen cases. The limitations to specific diagnosis, expressed in the foregoing, are accepted as applying fully to the cases of this series. The series is consecutive in that it includes all cases in which infectious mononucleosis was considered established with reasonable certainty by the existing criteria and which had one or more tests of liver function performed at random or in series. Most patients had two or more tests performed several times. During this period many other patients were encountered, some as outpatients, who probably suffered from this condition but they are omitted because of the absence of confirmatory laboratory data.

The heterophile antibody determinations were made by the method of Davidsohn.^{28,29} The absorption technic was employed. Liver function tests included icterus index, seventy-four cases; qualitative urine urobilinogen excretion, sixty-eight cases; cephalin cholesterol flocculation test, eighty-two cases; thymol turbidity test, seventy-seven cases; prothrombin time, thirty-nine cases and bromsulfalein dye retention, sixty-two cases. Urobilinogen excretion was considered abnormal if the urine dilution of 1:80 or more was positive by the Wallace-Diamond test.³⁰ For the cephalin cholesterol flocculation test values of +++ or more in twenty-four hours were interpreted as abnormal, and for the thymol turbidity test 4 units or more. The methods of Hanger and MacLagan, respectively, were used.^{31,32} Results of ++ and 2 units or more, respectively, for these tests are also recorded since these lower figures may be of significance.³³ The lowest normal value for prothrombin time was considered to be 75 per cent. The technic of Quick was used and the value expressed in per cent of normal.³⁴ For the early cases the bromsulfalein test was performed by the intravenous injection of 2 mg. of dye per Kg. of body weight, the amount retained in the blood being measured in twenty minutes. Significant retention rarely occurred. For the last forty-one cases an injection of 5 mg. of dye per Kg. of body weight was used and the per cent retained measured after thirty minutes.

With this method significant retention of dye was demonstrated frequently; a result of 10 per cent or more is listed as abnormal.

RESULTS

One or more liver function tests were abnormal in seventy-five of the eighty-three

TABLE I
SUMMARY OF THE RESULTS OF LIVER FUNCTION TESTS
DURING INFECTIOUS MONONUCLEOSIS IN EIGHTY-
THREE PATIENTS

Tests Made One or More Times	Total Cases	Results		
		Values (Maximum obtained in each case)	No. of Cases	Per Cent
Icterus index.....	74	10 units or more	28	38
		20 units or more	7	
Urobilinogen excretion....	68	1:80 or more	23	34
Cephalin cholesterol flocculation.....	82	+++ or more	70	85
		++ or more	76	92
* Initial test.....		+++ or more	60	73
		++ or more	71	87
Thymol turbidity.....	77	4 units or more	38	49
		2 units or more	58	75
† Initial test.....		4 units or more	27	35
† Initial test.....		2 units or more	47	61
Prothrombin time.....	39	Below 75% (Minimum 57%)	5	13
Bromsulfalein.....	62			
2 mg., 20 min. technic....	21	10% retention	1	
		5% retention	2	
		0% retention	18	
5 mg., 30 min. technic....	41	10% retention or more	20	49
		50% retention	2	
		40% retention	1	
		35% retention	5	
		30% retention	2	
		25% retention	1	
		20% retention	2	
		15% retention	3	
		10% retention	4	
		Less than 10% retention	21	

* The initial test (in some cases the only test) was made between the third and sixty-second day of disease, all but four before the eighteenth day.

† The initial test (in some cases the only test) was made between the third and seventy-ninth day of disease, all but six before the eighteenth day.

cases in this series. A general summary of the results and the comparative frequency of abnormal figures obtained with the various tests employed are presented in Table I. The data obtained in several representative individual cases is contained in Table II. Table III summarizes the findings in patients who had serial cephalin cholesterol flocculation and thymol turbidity tests made.

The cephalin cholesterol flocculation test was abnormal in 85 per cent of the eighty-

TABLE II
SUMMARY OF STUDIES IN FIFTEEN INDIVIDUAL PATIENTS WHO HAD SERIAL LIVER FUNCTION TESTS DURING
INFECTIOUS MONONUCLEOSIS

Patient Sex, Age, Onset	Date of Test	Blood		Hetero- phile Antibody Titer	Icterus Index (units)	Urine Urobil- inogen (Dilu- tion Positive)	Cephalin C: o- lesterol Floccu- lation	Thymol Tur- bidity (units)	Brom- sulfalein Reten- tion Per Cent	Pro- throm- bin Per Cent	Clinical			
		Total W.B.C. × 1000	Lympho- cytes Per Cent								Days in Hos- pital	Severity	Spleen Palpa- ble	Days of Fever 100°F. or over
M. K. F, 18	1/20/47	9.2	50	0	..	0	25	Mod.	0	10
	1/23	10.6	70	++				
	1/27	16.35	75	256	9	..	++++	3				
	2/5	8.9	56	++				
	4/4	9.0	26	..	7	..	0	0	..	100				
L. Y. M, 27	1/25/47	13.3	66	512	11	17	Mod.	+	9
	1/27	9	..	++++	80				
	1/29	5	..	++++	5	..	80				
	3/27	8.5	31	128	5	1:160	++++	5	0*	85				
	4/22	1:40	+	1				
P. S. F, 20	2/11/47	8.4	76	256	17	Mild	+	14
	2/21	10.95	68	..	5	..	++++	5	..	100				
	2/5/47	9.55	27	512	5	..	++++	5	0*	100				
	4/8	10.75	35	128	4	1:80	++++	3	..	100				
	4/29	64	..	1:10	++				
	9/25	8.6	36	..	10	0	++	0	0	..				
R. S. M, 19	2/20/47	9.3	83	1024	..	1:160	++++	4	..	66	20	Severe	+	9
	2/24	12.1	71	1:320	++++	6	0*	100				
	3/3	7.4	67	512	++++	5				
	3/19	9.0	62	512	6	1:40	++++	5	0	90				
	4/8	8.3	35	256	8	1:80	++++	1	..	85				
	4/22	0	..	1:40	+				
W. J. M, 20	2/18/47	18.0	81	256	16	Mod.	0	4
	2/21	5	..	+++	1	..	100				
	2/24	13.0	71	128	++++	2				
	3/19	8.6	44	64	10	1:20	+++	3	0*	100				
	4/8	7.0	53	32	7	1:40	+	1	..	100				
M. W. F, 20	2/26/47	9.65	76	1024	9	Mild	0	7
	3/1	16.15	67	..	9	..	+++	0	..	100				
	3/19	2.45	19	1024	4	1:40	+++	1	0*	100				
	4/8	9.0	30	512	4	0	0	1	..	85				
C. D. F, 21	2/26/47	11.5	82	2048	7	Mild	0	0
	3/3	10.2	63	1024	6	1:200	+++	1	..	100				
	3/19	6.65	51	1024	5	1:160	+++	5	0*	100				
	4/8	7.45	29	512	4	1:40	0	0	..	100				
	5/20	8.9	33	128	..	1:80	++	0				
M. E. F, 18	3/6/47	6.25	57	0	15	Mod.	+	8
	3/19	10.1	83	256	5	1:20	++++	5	0*	100				
	2/25/47	10.0	74	128	4	..	++++	7	0	100				
	4/8	8.5	37	32	6	1:40	++++	5	..	100				
	4/29	1:40	+++	2				
B. H. F, 24	8/15/47	7.	61	..	9	1:20	+	1	40†	...	3	Mild	0	2
	9/8	6.9	44	64	10	1:20	++++	5	0	..				
	8/10/47	1:20	0	2	0	..				
D. S. M, 23	8/18/47	20	68	256	10	1:60	++++	3	35†	...	20	Mod.	+	2
	9/4	7.5	28	..	10	1:20	++++	7	0	..				
	9/18	9	0	0	3	0	..				
	10/23	7	0	0	2	0	..				
C. E. M, 34	1/13/48	5.0	21	0	6	1:40	0	1	22	Mild	+	10
	1/15	6.0	47	256	6	..	++++				
	1/19	9	..	++++	3	15†	..				
	2/2	6	..	++++	2	0	..				
	2/13	0	0	1				
G. L. F, 18	1/14/48	18.9	73	0	++++	19	Mod.	+	0
	1/19	9	1:20	++++	5	0†	..				
	2/9	5.95	54	0	7	0	++++	3				
	3/30	7.0	22	..	5	..	++	1				
R. L. M, 19	2/7/48	11.0	78	0	30	1:320	..	5	18	Mod.	+	7
	2/9	20	..	0	5	30†	..				
	2/10	20	..	+++				
	2/16	8.85	78	128	10				
E. E. M, 20	3/4/48	8.0	69	0	7	1:80	++	2	0†	..	16	Mild	+	8
	3/9	12.0	50	128	++++				
	3/21	10	1:20	++++	5	0	..				
	4/9	7.0	52	0	5	1:20	0	3				
J. B. F, 19	3/19/48	20	52	512	25	1:80	+++	9	50†	...	19	Mod.	+	7
	3/25	9	73	..	12	1:40	..	9				
	3/29	6	40	+++				
	4/2	9	57	1:20	+	9				
	4/5	++++	..	0	..				

* 2 mg., twenty-minute method

† 5 mg., five-minute method

two cases in which it was done one or more times and on at least one occasion in thirty-eight of thirty-nine cases who had the test three or more times. A result of +++ or more was obtained in sixty of the eighty-two cases at the time the first test was made (in

TABLE III
INCIDENCE OF POSITIVE CEPHALIN CHOLESTEROL FLOCCULATION AND THYMOL TURBIDITY TESTS WHEN DETERMINATIONS WERE MADE SERIALLY IN PATIENTS WITH INFECTIOUS MONONUCLEOSIS

No. of Tests	Cephalin Cholesterol Flocculation			Thymol Turbidity				
	No. of Cases	Re-sult* +++ or More	Per Cent	No. of Cases	Re-sult* 4 Units or More	Per Cent	Re-sult* 2 Units or More	Per Cent
3 or more	39	38	97	29	19	66	26	83
2 or more	60	57	95	53	29	55	43	81

* Pertains to the highest value obtained in the series of tests in each patient.

some cases a single determination). The earliest day of the disease on which a cephalin cholesterol flocculation test was made varied in individual patients from the third to the sixty-second; all except four cases were tested before the eighteenth day. For the thirty-eight patients who had a series of three or more tests the average time from the estimated onset of the disease to the day on which the last result of +++ or more was obtained was thirty days. (Table iv.) For eight of these the final value was +++ or more at ten, fifteen, fifteen, twenty-three, twenty-six, thirty-two, fifty-six and sixty-three days, respectively. The duration of abnormal flocculation beyond this in these patients is unknown. Flocculation of ++ or more occurred on the average for forty-four days. During convalescence the interval between examinations was two to three weeks for many cases so that abnormal flocculation undoubtedly persisted longer on the average than these figures indicate. The cephalin cholesterol flocculation test was positive in twelve of the fifteen cases in which heterophile antibodies were not demonstrated. In nine of the twelve the

two tests were made at the same time. The possibility that infectious hepatitis of specific virus etiology may have been present in those cases in which heterophile antibodies were not demonstrated is difficult to eliminate. During the period of this study pa-

TABLE IV
DURATION OF POSITIVE CEPHALIN CHOLESTEROL FLOCCULATION AND THYMOL TURBIDITY TESTS IN PATIENTS WITH INFECTIOUS MONONUCLEOSIS WHO HAD A SERIES OF THREE OR MORE TESTS

Test	Result	No. of Cases	Average Days*	Maximum Days*	Minimum Days*
Cephalin cholesterol	+++ or more	38	30	79	6
flocculation	++ or more	38	44	290	9
Thymol turbidity	4 units or more	19	35	74	12
	2 units or more	25	52	253	14

* Number of days from onset of disease to day on which the last test with the result indicated was obtained. In eight of these patients the cephalin cholesterol flocculation was +++ or more at the time of the last determination, ten, fifteen, fifteen, twenty-three, twenty-six, thirty-two, fifty-six and sixty-three days, respectively. In four the thymol turbidity value was 4 units or more when last examined, twenty-three, twenty-three, twenty-eight and fifty days, respectively.

tients with clearly recognizable infectious hepatitis were rarely encountered.

The results obtained with the thymol turbidity test in seventy-seven patients are listed in the tables. It was positive in a significant proportion of cases but less frequently and, on the average, later in the course of the disease than the cephalin cholesterol flocculation test. The serum of four of the patients who had a series of tests showed values of 4 or more units when last examined at twenty-three, twenty-three, twenty-eight and fifty days, respectively. The thymol turbidity values were abnormal in seven of the fifteen cases in which heterophile antibodies were not demonstrated. Three of the seven had the tests made at the same time.

The icterus index was 10 units or more in twenty-eight (thirty-eight per cent) of the seventy-four cases in which it was made. Seven of these had 20 units or more. The increase in icterus index, when it occurred, was present during the early acute phase in most instances. The highest result obtained for the thymol turbidity test was less than 4 units in nine cases and for the cephalin cholesterol flocculation test less than +++

in three cases of the total of twenty-eight in which the icterus index reached 10 units or more. Thymol turbidity was positive in the other nineteen cases and cephalin cholesterol flocculation in the other twenty-five cases who had an elevated icterus index. Abnormal amounts of urobilinogen appeared in the urine in twenty-three (thirty-four per cent) of the sixty-eight cases in which the test was made. The prothrombin time was below 75 per cent of normal in five of the thirty-nine patients tested. It did not reach significantly low levels in any patient.

The bromsulfalein test was abnormal in twenty (49 per cent) of the forty-one cases in which the 5 mg. per Kg. dose of dye was employed and the retention in the blood measured after thirty minutes. In all of these an increased retention of dye occurred during the first test; in all but one case (retention 10 per cent) the first test was made during the first two weeks of illness. Table v summarizes the results of three tests in forty-one cases who had bromsulfalein (5 mg., thirty-minute method), cephalin cholesterol flocculation and thymol turbidity tests. Cephalin cholesterol flocculation was positive when bromsulfalein retention was abnormal in all but one case. It was positive in eighteen cases in which bromsulfalein retention was not increased. The results of thymol turbidity tests did not correlate closely with bromsulfalein retention. (Table v.)

A comparison of the results of the liver function tests made in this series of cases of infectious mononucleosis indicates that the cephalin cholesterol flocculation was most frequently abnormal. It was positive early and for a significant length of time in nearly all cases.

A prolonged period of fatigability frequently occurs following infectious mononucleosis. However, the duration of subjective symptoms did not correlate with the results of liver function tests for the twenty-four patients of this series on whom sufficient information for evaluation during convalescence is available. Most of the patients

returned to school before all of the liver function tests had become normal. (Table II.) Treatment consisted of bed rest during the febrile period, activity as limited during convalescence as was possible when University work was resumed, and a high-

TABLE V
CORRELATION OF THE RESULTS OF THREE TESTS IN FORTY-ONE PATIENTS WITH INFECTIOUS MONONUCLEOSIS*
(The Most Abnormal Result Obtained for All Tests in Each Patient Is Used)

Bromsulfalein Retention (5 mg., 30-min. technic)		Cephalin Cholesterol Flocculation		Thymol Turbidity	
Result	No. of Cases	+++ or More	Less Than +++	4 Units or More	Less Than 4 Units
		No. of Cases	No. of Cases	No. of Cases	No. of Cases
10% or more.....	20	19	1	10	10
Less than 10%.....	21	18	3	11	10

* In all except five patients the tests were made on the same day.

protein, high-carbohydrate, low-fat diet for as long as practicable. Patients who had bacterial or fusospirochetal pharyngitis or tonsillitis during the course of the disease received penicillin by intramuscular injection. A relapse or clinical evidence of chronic liver disease was not observed.

COMMENTS

In this series of eighty-three cases of infectious mononucleosis tests of liver function revealed abnormal values in a significant proportion. From the results obtained it is reasonable to suggest that every patient with this condition will demonstrate abnormal liver function, as measured by the tests employed, during its course. The studies of other investigators have resulted in a similar conclusion.²²⁻²⁵ However, the clinical significance of the results of these liver function tests during infectious mononucleosis as a measure of hepatic involvement or damage is not certain. As far as we are aware, fatalities due to liver insufficiency during this disease have not been observed. Long term studies of liver function following infectious mononucleosis are not available and must await the passage of time. Investiga-

tions to date have revealed the tendency of liver functions to return to normal within two to six weeks. De Marsh and Alt report cases with abnormal values at three and four and one-half months, respectively.²³ Abrams⁴³ reports a case with visible jaundice for eleven weeks; Cohn and Lidman suggest that a patient under their observation was developing chronic hepatitis.²² In our series the cephalin cholesterol flocculation test was abnormal after eight and nine weeks, respectively, in two patients whose further course is unknown. Experience suggests that liver damage sufficient to cause insufficiency in later life is infrequently if ever incurred as the sequel to hepatitis during infectious mononucleosis.

In the present series the tests most frequently abnormal were the cephalin cholesterol flocculation and thymol turbidity. These are dependent upon alteration in the serum globulin components.³⁵⁻³⁷ The factors responsible for abnormal values for these tests as well as for retention of brom-sulfalein are suspected to reside in cells of the reticulo-endothelial system.³⁸ In the strict sense these tests are not direct measures of liver function. Nevertheless conditions other than hepatitis have been associated infrequently with similar abnormalities.^{25,33,36,44} The mechanism operating for serum alkaline phosphatase increase, employed as a test of liver function by Gall, is open to similar criticism.^{24,39,40} The evidence to date indicates that the mechanism of excretion of urobilinogen is dependent upon the parenchymal cells of the liver. Urinary excretion of urobilinogen was abnormal in a significant proportion of cases (34 per cent) in this series. Of necessity, the Wallace-Diamond dilution technic was used instead of the more reliable quantitative estimation of urobilinogen developed by Watson. White and co-workers found that while significant discrepancies between these two methods are unusual, individual variations are seen with sufficient frequency to lessen the value of the Wallace-Diamond technic as a single test.⁴¹ Since an elevation of icterus index in individual cases is not conclusive evidence of hepatocellular injury, the frequent ob-

servation of this circumstance does not provide proof of hepatitis. However, when the results of all of the tests performed in individual cases of infectious mononucleosis are evaluated, it is reasonable to conclude that actual hepatitis occurred in a significant proportion of the cases in this and other reported series. This conclusion is supported by the demonstration of hepatitis, as well as involvement of many other organs, in all of the postmortem studies which have been made.¹²⁻¹⁴

The problem of infectious mononucleosis is important because of its frequency and the evidence that many organs may be involved during the course.¹⁻¹¹ The reports that severe central nervous system involvement may be associated with this syndrome are of particular significance.^{4-10,14} The disease warrants intensive investigation from this standpoint. The spinal fluid was normal in the two cases of the present series in which it was examined.

Infectious mononucleosis is protean in its manifestations and diagnosis is often difficult. It may be responsible for many apparently minor illnesses. Since the etiology is unknown, the diagnosis at present must depend upon clinical judgment, blood examination and measurement of the heterophile antibody rise in the serum. Of these the only reasonably specific aid is the heterophile antibody test. The demonstration of an increase in heterophile antibodies is often difficult and exacting laboratory technics are required.^{28,29} A rise in heterophile antibodies is not usually present until after the first week of the disease. The titer falls rapidly in many cases and may be overlooked if serial tests are not made. Because of these considerations, several cases in the present series are included in spite of failure to demonstrate a rise of heterophile antibodies in the serum. Of diagnostic importance is the fact that a rise in heterophile antibody titer is not a recognized feature of infectious hepatitis of known virus etiology.²⁶

During infectious mononucleosis the cephalin cholesterol flocculation test becomes abnormal in the first few days of the disease in nearly all cases. It was positive in twelve

of the fifteen cases in which heterophile antibodies were not demonstrated. As suggested by Evans²⁵ this test often provides earlier and more uniform confirmatory evidence for the presence of infectious mononucleosis than the heterophile antibody determination if infectious hepatitis of viral etiology can be eliminated.

In our experience and that of others the differentiation between infectious mononucleosis and infectious hepatitis in occasional cases with or without jaundice has been difficult if not impossible by either clinical or laboratory means.^{9,10,25,26,27} As a result it is likely that mistakes in the diagnosis of these conditions are of frequent occurrence. Every patient included in this series was evaluated in the light of this possibility, especially when cases with positive cephalin cholesterol flocculation and a negative heterophile antibody titer were encountered. It is believed that the differentiation has been as accurate as present knowledge and the methods employed permit. The uncertainty which still exists is further evidence of the similarity which is not infrequently exhibited by these diseases. In spite of the failure to demonstrate a correlation between abnormalities of liver function and the persistence of symptoms during infectious mononucleosis, it seems reasonable to manage patients with this disease by carefully controlled activity and diet in the manner shown to be beneficial for the treatment of infectious hepatitis. Further, since the etiology of infectious mononucleosis has not been clarified, it would seem logical to employ the methods which have been successful in recognizing the specific etiology of infectious hepatitis to the study of infectious mononucleosis.

SUMMARY

The results of tests of liver function performed at random or in series during the course of infectious mononucleosis in eighty-three patients are presented. Abnormal values were obtained in seventy-five. Of the tests employed the cephalin cholesterol flocculation was positive most frequently. A value of +++ or more was obtained in

thirty-eight of thirty-nine patients who had a series of tests. This persisted for an average of thirty days. Thymol turbidity values were 4 units or more in nineteen of twenty-nine cases (65 per cent) in which a series of tests was made. It remained positive for an average of thirty-five days. The icterus index was 10 units or more and the urobilinogen excretion abnormal in over one-third of the cases examined. Bromsulfalein retention (5 mg., thirty minute-technic) was 10 per cent or more in twenty of forty-one cases (49 per cent). The usefulness of these tests in indicating the presence of hepatitis is considered. The available evidence would seem to justify the conclusion that true hepatitis occurs in a significant proportion of all cases of infectious mononucleosis.

In this series a relapse of acute symptoms or clinical evidence of chronic liver disease was not observed. Some patients whose subsequent course is unknown had abnormal liver function tests when they were last examined. The cephalin cholesterol flocculation test was positive more uniformly than the heterophile antibody determination. When infectious hepatitis of viral etiology could be eliminated with reasonable certainty, it proved to be a valuable aid in the early diagnosis of infectious mononucleosis.

Accurate differentiation between infectious mononucleosis and infectious hepatitis of virus etiology with or without jaundice was found to be impossible in occasional cases. In agreement with the conclusions of other investigators it is suggested that patients with infectious mononucleosis should be treated in the manner known to be beneficial for the management of infectious hepatitis.

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Endocrinopathies Associated with Hyperostosis Frontalis Interna*

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THICKENING of the internal table of the frontal bone occurs more frequently than is generally supposed, and associated with it there are usually some metabolic, endocrine, neuropsychiatric or hypertensive manifestations. When one or more of these abnormalities are present with hyperostosis frontalis interna, a syndrome is formed which is sometimes called "metabolic craniopathy," Morgagni syndrome or Stewart-Morel syndrome.

Although the characteristic thickening in the frontal bone had been observed in museum specimens since ancient times, and Morgagni¹ noted the syndrome of obesity, virilism and thickening of the bone in 1765, the modern concept of its clinical significance was initiated in 1928 after Stewart² reported three cases of the syndrome diagnosed at autopsy. However, the first living person with hyperostosis frontalis interna was reported by Morel³ in 1930, and only three living people with the disease^{4,5} had been reported up to 1936 when Henschen⁶ diagnosed twenty-eight cases. In 1935 to 1936 Moore⁷⁻⁹ reviewed 6,650 roentgenograms of the skull, about one-half of which were taken on females, and found that the films of 3.4 per cent of the patients showed some evidence of thickening of the inner table. He checked the case records of 193 patients, making a personal study of six patients and found that certain nervous and metabolic symptoms were more prevalent than in hospital and clinic patients in general. Since then several articles have appeared in the literature with discussions of from one to sixty-six cases.¹⁰⁻²⁷

Various theories have been advanced

regarding the cause of this condition, but none of them fits all the cases. Pituitary dysfunction, among other things, has been suspected. There is no evidence at the present time that pituitary disease produces hyperostosis and it must be stated that the etiology is unknown.

Although endocrine disease has been mentioned as being a part of the syndrome by many writers, very little detail has yet been given. The purpose of this paper is to show the frequency of endocrine abnormalities and their relationship to other findings as they were observed in our patients with hyperostosis frontalis interna. It is an analysis of ambulatory patients seeking office treatment.

ANALYSIS OF CASES

Seventeen cases were found, all in women. They were located by watching for the condition among the last 251 patients having roentgenograms made of their skulls for the endocrine department. Twenty-six females under the age of eighteen and thirty-seven males showed no evidence of the abnormality. A control group of thirty-eight non-obese females over the age of eighteen had normal-appearing skulls. Of the 150 obese women over the age of eighteen, part of whom had a psychoneurosis, seventeen or 11 per cent had some degree of hyperostosis frontalis interna. Of all women over the age of eighteen for whom films of the skull were made 9 per cent had this condition.

The diagnosis was always proved by taking x-ray pictures of the skull. In a few instances the diagnosis was made prior to seeing the films. Because of the protean

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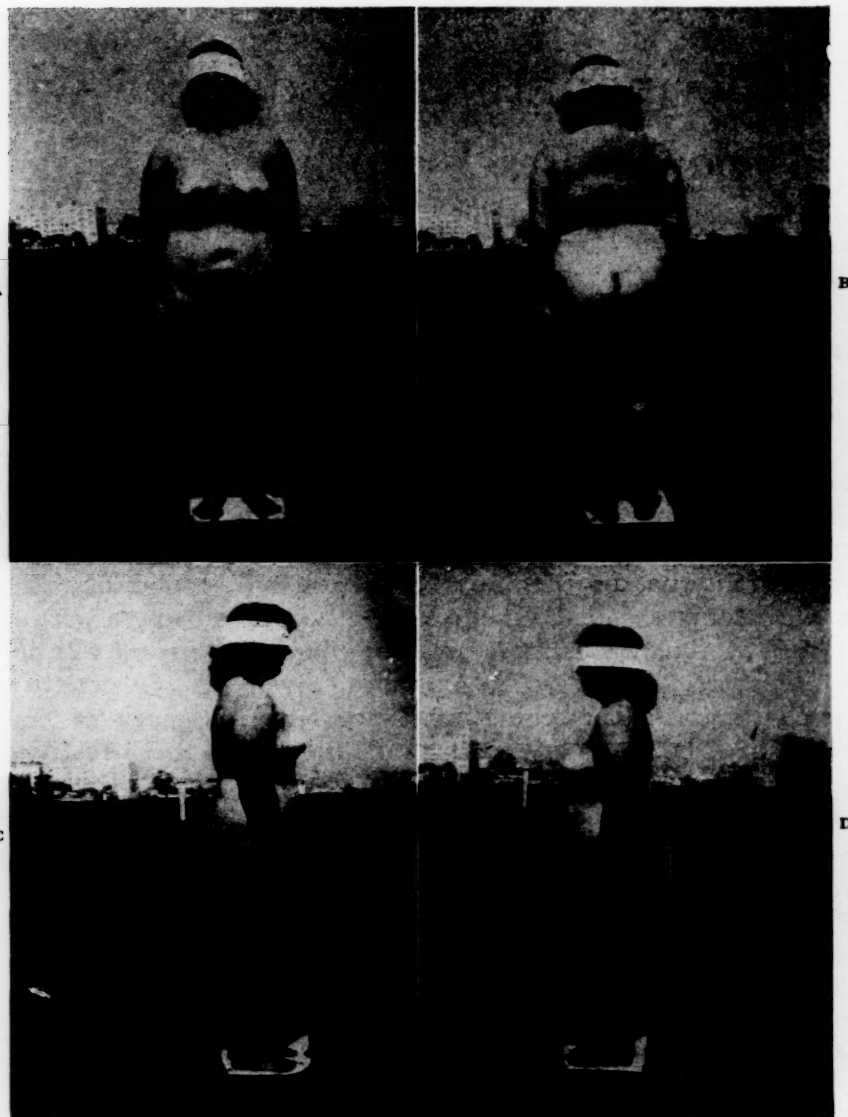


FIG. 1. A to D, Miss M. M., Case XI after losing weight from 210 to 160 pounds by dieting.

nature of the disease, it was difficult to make a diagnosis without the x-ray findings. (Figs. 1 to 5.)

The ages of the patients ranged from eighteen to fifty-two years. A total of eighteen children had been born to ten women. There was one single girl. The other six married women had no children.

The following diagnoses of endocrine disease were made: diabetes mellitus, two cases; myxoedema, one case; non-toxic goiter, one case; hyperthyroidism (prior to thyroidectomy), one case; secondary amenorrhea, two cases; menopause due to radium

therapy, one case; menopause due to x-ray therapy, one case; climacteric-natural, two cases; artificial menopause (surgical), four cases; sterility (anovulatory), two cases and bilateral cystic ovaries (surgical diagnosis during an appendectomy), one case.

In addition, there were two cases of probable hypothyroidism and one case of possible hypothyroidism. One patient had exophthalmos. The vaginal smears were changed by infections, previous treatment, etc., but they showed evidence of estrogen deficiency in several patients. Ten of the sugar tolerance tests showed a slight in-



FIG. 2. Case XI; hyperostosis frontalis interna.



FIG. 3. Case III; hyperostosis frontalis interna.

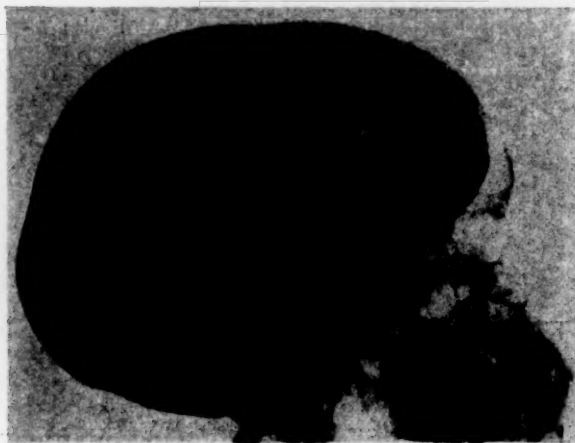


FIG. 4. Case V; hyperostosis frontalis interna.



FIG. 5. Case XIII; hyperostosis frontalis interna.

crease in the amount of blood sugar in one or more of the determinations, possibly due to a pituitary disorder, a tendency to develop diabetes mellitus, abnormal liver function or other glandular disorders. (Table I.) Some of these figures were without doubt normal as they were within the range of findings that could be normal. Two patients had sugar in their urine. Several members of the family of one of the diabetic patients had diabetes mellitus.

Numerous symptoms and signs of possible endocrine importance were noted. (Table II.) The basal metabolic rate was above plus 10 for one patient and below minus 10 for seven. The clinoid processes of the sella turcica of four patients were bridged. A hysterectomy had been per-

formed on four patients. The height ranged from 59 to 68 inches and averaged 63 inches. The weight varied from 109 pounds to 280 pounds. The weight was normal for the height and age in only three patients, but they had dieted strictly for years to keep their weight down. The other fourteen women had 709 pounds of excess weight, averaging 50 pounds per patient. A record of family obesity was found in ten case histories. The blood pressure was above normal in seven patients. The blood calcium was normal for the eight patients tested. Four blood cholesterol tests were high enough to be considered in a diagnosis of

mild hypothyroidism, i. e., 198, 210, 210 and 270. The only test that was definitely elevated, however, was the latter one. Blue striae were found on two patients, suggesting pituitary involvement. Eight patients were no longer menstruating, one having

cardia, paresthesias, flatulence, epigastric distress, mastalgia, psychalgia, nocturia, frigidity, difficulty in thinking and concentrating, indecision, pruritus of the labia majora, nightmares, phobias and tinnitus. Other unpleasant symptoms were described

TABLE I
BLOOD CHEMISTRY: SUGAR TOLERANCE * AND OTHER TESTS

Case No.	Name	Fasting Blood Sugar	One-half Hr.	One Hr.	Two Hr.	Sugar in the Urine	Cholesterol†	Calcium‡
I	C. S.	207	2 plus	176	11
II	B. F.	134	...	170	165	3 plus-1 hour	150	
III	B. J.	Negative		
IV	F. C.	94	111	118	108	Negative	141	12
V	S. M.	101	185	175	133	Negative	270	
VI	M. W.	104	158	158	94	Negative		
VII	H. C.	115	149	143	134	Negative	132	11.5
VIII	F. B.	103	122	111	101	Negative	210	11
IX	B. B.	210	4 plus	150	
X	I. S.	143	221	184	164	Negative	138	11
XI	M. M.	92	117	127	104	Negative	129	
XII	E. B.	103	155	161	128	1 plus-1 hour	165	10
XIII	L. B.	126	134	125	123	Negative	147	
XIV	G. R.	104	150	158	137	Negative	198	
XV	J. T.	93	151	108	86	Negative	210	
XVI	M. I.	109	141	109	...	Negative	180	12
XVII	E. A.	103	158	131	85	Negative	135	11

* The Folin-Wu method.

† Reported as mg. in 100 cc. blood plasma.

‡ Reported as mg. in 100 cc. blood serum.

stopped at the age of nineteen. This latter patient is now fifty years old. Five patients menstruated every twenty-eight days, whereas three had late periods and one bled semimonthly. Eight patients had dry skins but one woman had profuse perspiration. Seven patients had dry hair and five had brittle nails. Eleven patients were bothered by hot flushes. Six patients complained of feeling too cold. Thirteen patients had some hirsutism although in five it was slight. Six patients had had dysmenorrhea during the menacme.

Other symptoms are listed in Table III. Most of the patients were forgetful and some of them had trouble thinking of the right word to say. Many complained of various symptoms, such as palpitation, dyspnea, polyphagia, somnolence, insomnia, backache, precordial pain, scotomas, tachy-

by the patients in the following manner: "difficult to get a satisfying breath," "legs cramp," "something snaps and I feel as if I am on a different plane," "jerking of muscles all over the body," "spells of anger," "quiver all over," "lost strength in the left arm" and "a burning spot the size of a dollar on each buttock."

The following diseases were also diagnosed: asthma, allergic rhinitis, urticaria, vitiligo, epilepsy, secondary anemia, neurodermatitis and pseudocyesis.

Most of the patients were psychoneurotics and had had nervous breakdowns. There was a high rate of morbidity with considerable remission and exacerbation of the symptoms.

TREATMENT

No effective treatment is known for the hyperostosis. For diseases associated with it

specific treatment was frequently given. For instance, myxoedema and symptoms of hypothyroidism responded to thyroid extract. There was great improvement with complete relief of hot flushes in the menopausal or estrogen-deficient patient when

the caloric content was decreased. A minimum amount of protein was allowed. This limited choice of foods resulted in a diet consisting largely of fruits and vegetables, the sugar content of which stimulated the pancreas to produce more insulin. The benefit

TABLE II
CLINICAL AND LABORATORY DATA OF POSSIBLE ENDOCRINE IMPORTANCE

Case No.	Age	Weight	Height in Inches	Blood Pressure	Children	Menses	Surgery or Therapy	Vaginal Smears		Hot Flushes	Too Cold	Dry Skin	Dry Hair	Brittle Nails	Basal Metabolic Rate	Goiter	Hirsutism	Hyperostosis Frontalis Interna
								G	C									
I	45	270	67	166/100	3	0	X I OY	+	+	++	+	+	+	+	+18	0	+	+
II	37	154	62	130/96	2	R	+++	+++	0	0	0	0	0	-14	0	+	+
III	36	176	60	166/94	1	R	++++	+++	0	0	+	+	0	-5	0	+	+++
IV	50	280	67	154/110	1	0	+	++	+	0	0	0	0	-25	0	++	++
V	38	109	62	114/64	0	0	2 OY H	++	++	++	0	0	+	0	-13	0	0	++
VI	40	122	62	130/90	1	I	+++	+++	+	0	0	0	0	-1	0	+	+
VII	30	164	67	120/70	0	I	+	++	0	+	0	-11	0	0	+++
VIII	43	168	60	120/70	0	0	++	0	0	0	0	-16	0	0	+
IX	51	160	59	208/100	3	0	Ra	++	0	0	0	+	-4	0	++	++
X	33	172	62	118/84	2	R	+	++	0	0	0	0	0	-11	0	++	+
XI	18	210	63	104/64	0	I	0	+	+	0	+	-18	0	++	++
XII	52	245	68	164/116	2	R	+	+	0	0	+	0	0	-4	0	0	+
XIII	31	148	63	120/74	0	R	+++	++++	0	+	+	+	0	-26	0	++	++
XIV	51	162	60	125/82	1	0	H	++	++	0	+	+++	++	+	+9	T	+	++
XV	46	165	67	150/100	0	0	H	++	+++	+	0	+	0	+	-5	+	++	+
XVI	38	164	61	222/120	0	I	+++	++	+	+++	++	++	0	-1	0	+	++
XVII	43	137	61	110/70	2	0	H	++	++	+	0	0	0	0	+1	0	+	+

R—Regular

I—Irrregular or late

X—X-ray therapy to ovaries

Ra—Radium therapy intrauterine

I OY and 2 OY—Unilateral and bilateral oophorectomy

H—Hysterectomy

G—Glycogen in vaginal smears

C—Cornification of vaginal cells

+—Slight cornification of cells

++++—Complete cornification of cells

T—Thyroidectomy

hexestrol or conjugated estrogens—equine were given in effective oral doses. Diabetes mellitus was controlled by insulin and hyperthyroidism was corrected by thyroidectomy. Obesity responded to a low caloric diet even though it appeared to be on an endogenous basis. The low sugar tolerance, as shown by a greater than average increase in blood sugar, was improved by a low fat diet and if the patient was also overweight

obtained with this method was demonstrated by Case XII. Before treatment this patient had the following sugar tolerance: fasting, 103; one-half-hour, 155; one-hour, 161 and two-hour, 128 with some sugar in the first and second-hour urine specimens. After treatment there was less sugar: fasting, 109; one-half-hour, 138; one-hour, 126; three-hour, 63 and five-hour, 72 with the urine test negative for sugar. Actually the three-

hour specimen was a little low, probably due to overproduction of insulin. In Case VII there was a response similar to that in Case XII with the following sugar tolerance before treatment: fasting, 115; one-half-hour, 149; one-hour, 143 and two-hour, 134.

TABLE III
SYMPTOMS

Symptom	No. of Patients
Nervousness.....	16
Asthenia.....	16
Weakness.....	15
Dizziness.....	15
Headache.....	14
Mental depression.....	13
Poor vision.....	12
Giddiness.....	11
Diplopia.....	3

After treatment the blood sugar readings were lower: fasting, 92; one-half-hour, 112; one-hour, 120; three-hour, 96 and five-hour, 82.

Some of the patients required symptomatic treatment. Phenobarbital allayed the nervousness and mental depression. Gynergen was helpful for the headaches.

It was explained that many of the symptoms were due to the accompanying neurosis and, unless severe, should be ignored. Some practical advice was given concerning the psychoneurosis.

COMMENT

Morbidity, headache, forgetfulness, asthenia, vertigo, obesity, poor vision and either psychoneurosis or psychosis occur too frequently with hyperostosis frontalis interna to be coincidental. The fact that this condition is found almost exclusively in the female is also important. In our series of cases there was a high rate of endocrine disorders which, of course, may have been coincidental in the small number of patients. However, the findings are important in that they show the need for making complete endocrine studies on these patients as well as a very thorough history and general examination.

A study of the literature as well as the present series of cases convinces one that these patients have many disturbances of a varied nature. There is some similarity in

the group as a whole but considerable individual difference. Possibly the cause of metabolic craniopathy produces changes in different parts of the system and the symptoms vary according to the parts involved. For instance, there are areas of atrophy in the frontal lobes and sometimes other parts of the brain. This degeneration occurs mostly in the so-called "silent area," and the bone protrudes into the involved parts. The variation in the amount and location of cerebral involvement may determine to some extent the amount of forgetfulness, headache, etc. The disease may occasionally cause trouble in the hypothalamus with resultant obesity and/or primary pituitary disturbance with secondary thyroid, ovarian or adrenal involvement.

It has been stated that the pituitary gland may be responsible for this disease. This idea developed, at least in part, from the opinion previously believed but now thought to be incorrect that obesity of the type seen in these patients is due to a disturbance in pituitary function. It seems improbable that hyperostosis frontalis interna is caused by any type of abnormal pituitary function as it is not consistently found with any known type of pituitary disease.

There is a similarity in the appearance of these patients because the obesity is usually of the rhizomelic type. The pictures shown in the literature are mainly of this type. However, Tager et al.¹⁴ found the weight to be above normal in only twenty-six of sixty-six patients studied by them. Nevertheless, even in their group of patients the percentage of obesity was greater than in the general population.

It is reported that hyperostosis frontalis interna is sometimes found in normal asymptomatic individuals. Possibly the bony changes have preceded the appearance of symptoms. According to the literature available,¹⁻²⁷ the incidence of this condition in otherwise normal women is quite low. None of our patients could be classed as normal.

A thorough study of the patient with the consultation of specialists for diagnosis of

definite abnormalities will avoid treatment for diseases not present. A careful explanation of the condition will prevent the patient from continuously seeking new remedies from numerous doctors.

SUMMARY

The findings in seventeen women with hyperostosis frontalis interna have been tabulated and discussed. Evidence of some endocrine abnormality was frequently found but was possibly coincidental. There was great similarity of body build and symptomatology in this group of patients. As abnormal findings were numerous thorough laboratory study and detailed physical examination were essential; consultations with other specialists were frequently advisable.

Frontal headache, asthenia, forgetfulness, vertigo, nervousness, obesity and poor vision were rather characteristic of this group. There was a high degree of morbidity with frequent remission and exacerbation of symptoms.

No cause was found for this disease. It was limited almost entirely to the adult female. Some of the symptoms were probably due to cerebral atrophy.

Useful hormonal, dietary and symptomatic treatment was discussed.

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Subacute Bacterial Endocarditis*

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WITH the advent of the use of penicillin in the treatment of bacterial infections, a new era began in medicine. Subacute bacterial endocarditis, which was more than 99 per cent fatal only a few years ago, can now be cured in a large percentage of cases.

were considered in this series. Other organisms can cause subacute bacterial endocarditis but for strict clinical accuracy two cured cases of endocarditis due to staphylococci have been eliminated.

Six females and four males were treated, ranging in age from sixteen to sixty-one

TABLE I
SUBACUTE BACTERIAL ENDOCARDITIS

Case	Age	Sex	Valve Involved	Probable Precipitating Factor	Organism	Required Effective Penicillin Dose	Total Penicillin	Complications	Hospital Days	Previous Treatment
1	32	F	Mitral	Rheumatic flare-up	<i>Streptococcus non-hemolyticus (ignavus)</i>	100,000 units every 3 hr.	31,000,000	None	45	None
2	59	M	Mitral	?	<i>Streptococcus non-hemolyticus</i>	75,000 units every 3 hr.	32,850,000	Embolus to central retinal artery, blindness	39	None
3	19	M	Mitral and aortic	Boil on face	<i>Streptococcus non-hemolyticus</i>	75,000 units every 3 hr.	16,000,000	None	46	None
4	16	F	Mitral	Respiratory infection	<i>Streptococcus non-hemolyticus (mitis)</i>	200,000 units every 2 hr.	84,100,000	Cerebral embolus, right hemiplegia	67	None
5	17	F	Congenital defect	Tooth extraction	<i>Streptococcus non-hemolyticus (salivarius)</i>	200,000 units every 3 hr.	49,550,000	Multiple pulmonary emboli	52	None
6	23	F	Aortic and mitral	Respiratory infection	<i>Streptococcus non-hemolyticus (mitis)</i>	100,000 units every 3 hr.	20,750,000	Emboli to fingers	49	Yes
7	52	M	Aortic and mitral	Abscess of teeth	<i>Streptococcus non-hemolyticus (mitis)</i>	100,000 units every 3 hr.	41,800,000	Congestive heart failure	68	None
8	52	M	Mitral	Tooth extraction	<i>Streptococcus non-hemolyticus (salivarius)</i>	100,000 units every 3 hr.	38,400,000	Emboli to fingers, toes, scotomata in visual field	62	Yes
9	27	F	Aortic and mitral	Tooth extraction	<i>Streptococcus non-hemolyticus</i>	200,000 units every 3 hr.	50,000,000	None	48	None
10	61	F	Mitral	Tooth extraction	<i>Streptococcus non-hemolyticus (mitis)</i>	50,000 units every 3 hr.	10,950,000	None	38	None

We wish to add to the literature our own experience in the treatment of all the proven cases of subacute bacterial endocarditis admitted to the Presbyterian and Woman's Hospitals for the year 1946. (Table I.) These cases comprise ten patients, all of whom obtained clinical cures and continued to have negative blood cultures since their discharge from the hospital. Only those patients with positive blood cultures for the non-hemolytic streptococcus

years. Six patients, five of whom were females, were in the age group from sixteen to thirty-two. The remaining patients were ages fifty-two, fifty-two, fifty-four and sixty-one, respectively, three of whom were males. With rare exceptions, subacute bacterial endocarditis occurs in patients with pre-existing valvular or congenital heart disease. Only three of the ten patients gave no history of previous heart disease. One of these three, however, gave a history of

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scarlet fever and "growing pains." Upon admission this patient had a rough, loud systolic murmur of mitral insufficiency. One patient had been a "blue baby" and had a definite diagnosis of heart disease made at the age of six years. The oldest patient, age sixty-one, had influenza in 1918 and had known of her heart murmur since that time although she remained symptom-free until the present illness. Another patient, age fifty-two, with mitral insufficiency first learned of his heart murmur at the age of forty. He had no definite rheumatic history but likewise had "flu" in 1918. One patient had mitral valvular disease for ten years and had taken digitalis during this entire period but had no definite rheumatic history. Two of the remaining patients, ages nineteen and twenty-three, had recurrent attacks of rheumatic fever. The last patient, aged fifty-two, had rheumatic fever as a young adult and was told he had an enlarged heart at the age of thirty.

Valvular defects in this series were found in five patients in whom only the mitral valve was diseased. Four patients had lesions involving the mitral and aortic valves; one had a congenital defect believed to be a patent ductus arteriosus.

With the predisposing factor of chronic valvular heart disease or congenital heart disease, the precipitating factor in the actual pathogenesis of subacute bacterial endocarditis is the presence of bacteremia which permits the bacteria to localize on the defective valve or congenital defect. Asymptomatic bacteremias have been proven to occur more frequently than was previously believed. It has been demonstrated that transient asymptomatic bacteremias occur after tooth extraction or dental manipulation done during the repair of teeth. Less common bacteremias that are asymptomatic occur after tonsillectomy and other operative procedures. Many patients with subacute bacterial endocarditis gave a history of recent simple respiratory infections. In this series of ten patients five had dental work with tooth extraction just prior to the onset of their illness. One had a history of

a "boil" on the face and "sinus trouble." Two had upper respiratory infections. One had a chronic cough and an episode of gall-bladder colic with transient jaundice prior to the onset of his illness. One patient gave a history suggestive of a recurrence of rheumatic fever with polyarthritides.

The earliest symptoms were those of a non-specific low grade infection. They complained of malaise, weakness, low grade remittent fever, chilly sensations and sweating which occurred most frequently at night. Cough, pleurisy and pains in the joints and muscles were also frequent complaints. Later in the course of the illness they developed symptoms produced by the embolic phenomena, such as sore fingers and toes with splinter hemorrhages or development of a blind spot in the visual field. The longest duration of symptoms before admission to the hospital was three months. The average was two to three weeks. Because of the vagueness and variability of symptoms and the insidious onset of this disease, it is essential to obtain repeated blood cultures in any patient with chronic valvular or congenital heart disease who presents himself with fever or unexplained symptoms.

The absolute diagnosis of subacute bacterial endocarditis can only be made in the presence of positive blood cultures. Before treatment is instituted it is essential to obtain positive cultures since it is usually impossible to obtain positive cultures while the patient is receiving penicillin even with penicillinase in the culture media. Rational treatment requires a knowledge of the organism and its sensitivity to the therapeutic agent. If the sensitivity of the organism to penicillin is known, one has some idea of the prognosis and the probable dosage required to achieve a cure. An organism highly resistant to penicillin will be difficult to eradicate even with large doses of penicillin, and the use of sulfonamide drugs combined with penicillin must be considered. If the individual has received penicillin or a sulfonamide drug prior to admission to the hospital, it may require

several days for the blood concentration to fall to a level which will permit the organism to grow. At least two cultures should be taken each day, one in the morning and one in the afternoon. If a marked elevation of temperature or an embolic phenomenon occurs, one should obtain a blood culture at such a time. Cultures should be taken aerobically and anaerobically since many of these organisms are micro-aerophils and will grow only in an atmosphere of reduced oxygen tension. Frequently the explanation for failure to obtain positive cultures is the fact that the organism must be grown anaerobically and only aerobic cultures were made. With a history of the use of a sulfonamide preparation or the use of penicillin, para-aminobenzoic acid or penicillinase, or both, must be incorporated in the media. The colony count on the pour plate should be done since it is of some value in estimating the severity of the infection.

Most of the patients in this series were started on an initial regimen of 50,000 units of penicillin every three hours, but in all but one the dosage had to be increased during the course of treatment. Two patients had the dosage increased to 75,000 units every third hour; four eventually received 100,000 units every third hour and three received 200,000 units every three hours. (One of the latter group actually received 200,000 units every two hours.) The dosage was increased due to persistence of fever, the report of persistently positive blood cultures, the presence of blood penicillin levels that were too low to inhibit growth of the particular organism involved or the occurrence of embolic phenomena. Several patients infected with resistant organisms during portions of their treatment were given bolstering doses of penicillin several times daily in the form of penicillin in oil and beeswax (300,000 units twice daily) or simply additional intramuscular injections of 200,000 units in addition to the regularly scheduled doses. The smallest total dosage used was 10,950,000 units and the largest dosage was 84,000,000 units, the

average dosage being 38,000,000 units. The large dose of 84,000,000 units was used in a girl aged sixteen who had an infection with a resistant organism and who during her illness developed a cerebral embolus.

The sensitivity of the organism to penicillin was variable. The least resistant organism encountered in this series required .625 units per cc. of culture medium for inhibition of growth. This level was easily achieved in the patient's serum. Some of the organisms encountered, especially in those who had probably been treated with inadequate doses of penicillin, developed such resistance that they continued to grow in culture media containing 20 units penicillin per cc. Although serum levels of this height never were maintained with doses of penicillin as just described (organisms continued to grow in undiluted serum samples taken midway between injections of penicillin), two patients infected with these penicillin resistant strains achieved clinical and laboratory cures.

Hospitalization of these patients averaged 51.4 days with the shortest period of hospital stay being thirty-eight days and the longest sixty-eight days.

It has been difficult in the treatment of these patients to decide when penicillin can be safely stopped. No absolute rules can be laid down and probably what one must rely upon is clinical judgment. Criteria for cure have yet to be established. However, one may arbitrarily say that these patients should receive treatment for at least a two-week period after they have become afebrile. Blood culture (with penicillinase) should remain negative and the erythrocyte sedimentation rate should be either normal or show a definite tendency in that direction. It is recommended that blood cultures should be taken at monthly intervals for a period of one year since a persistently negative culture is the proof of cure.

We have chosen the intermittent intramuscular method of administration as the most practical for routine hospital use. Either crystalline penicillin may be used or

the more slowly absorbed procaine penicillin preparations.

Some disadvantages of the continuous intravenous method are: (1) It is technically difficult to maintain. (2) The requirement of relatively large quantities of intravenous fluids over many days which may disturb the fluid and electrolyte balance of the cardiac patient who is obviously most intolerant to these changes and who can readily develop congestive failure. (3) The possibility of phlebothrombosis is great with intravenous therapy and this is an increased hazard to the bedridden patient. (4) Non-specific pyrogen febrile reactions may occur and may be difficult to differentiate from an exacerbation of the disease itself.

Technical difficulties in use of continuous intramuscular penicillin are such that there is no advantage over intermittent administration, especially in view of the now available purified crystalline forms that may even be given subcutaneously with small hypodermic needles.

Anticoagulants were not used in this series of cases for several reasons: The increased tendency to hemorrhage induced by heparin and dicumarol is an additional danger to the patient, and their use is not justified in view of recent reports in the literature which have cast doubt upon their value in the therapy of subacute bacterial endocarditis. Since heparin must be given either by frequent intravenous injection or by the rather painful intramuscular injection of Pitkin's menstruum, it adds a burden to a patient already receiving numerous injections of penicillin. Anticoagulant therapy also adds to the cost and inconvenience, both to the patient and to the laboratory as daily prothrombin times and frequent urinalyses are required. Prolonged heparin therapy is expensive and this money may be used to a better advantage in providing more prolonged treatment with penicillin.

Common complications may be divided into three groups: i.e., those resulting from emboli, congestive heart failure and rupture

of a heart valve. Perhaps one should also include complicating factors such as allergy to the therapeutic agent as manifest by fever and skin rashes. This is especially true of the urticarial type. Of the embolic phenomena perhaps the most serious complications are emboli to brain, eyes and mesenteric vessels. Now that the survival period has become longer, more cases of congestive failure have become evident. This seldom was seen previously since patients succumbed to the toxemia early in the disease. In our series there have been complications in five of the patients. They were cerebral embolus with hemiplegia, embolus to the central retinal artery with resulting blindness, appearance of a scotoma in the visual field, congestive heart failure and one case of urticaria secondary to penicillin therapy. This latter condition was remedied by a change in the brand of penicillin.

Any known foci of infection are best removed during the course of treatment when blood levels of penicillin are at a maximum. However, removal of foci of infection is not recommended until control of the disease has been accomplished. Ideally this should be done toward the latter part of treatment, at which time there is some hope that the bacteria at the focus itself may possibly have been eradicated by prolonged high concentration of the drug. Every effort should be made to prevent subacute bacterial endocarditis which is so damaging to the health of the victim and which produces such great economic loss. Although little can be done to eliminate the predisposing factor (i.e., valvular damage from rheumatic fever or a congenital defect), it is believed that in many cases it can be prevented by watching for foci of infection and, particularly, by use of sulfonamide drugs or preferably penicillin before, during and after removal of these foci. This is especially true in manipulation or extraction of teeth as is shown by the fact that five of the ten patients herein reported had had recent previous dental work. On the ward service of this hospital those patients who have infected teeth with or without

cardiac lesions, or any patient with a cardiac lesions as just described is given penicillin for at least a twelve-hour period before and forty-eight hours after dental extraction usually in doses of 20,000 units every three hours. Sulfadiazine also may be used providing an adequate blood level has been reached prior to the time of removal of the focus and that it is maintained for a period of at least forty-eight hours thereafter. Penicillin in oil and beeswax may be used giving 300,000 units the day before, the day of and the day following the operative procedure.

SUMMARY

1. In the year 1946 ten patients with subacute bacterial endocarditis due to non-hemolytic streptococcus were admitted to this hospital. All have achieved cures with the use of penicillin.

2. Five of the ten patients had had recent dental work prior to onset of the illness which probably precipitated the infection.

3. Treatment should not be started until a positive blood culture is obtained and the organism isolated for further study.

4. Both aerobic and anaerobic blood cultures should be made.

5. Patients should be started on a minimum of 75,000 to 100,000 units of penicillin every three hours since in this series smaller doses were found inadequate. The minimum daily dose that should be administered is at least 600,000 units of penicillin per twenty-four hours. This also may be given in the form of slowly absorbable, procaine penicillin preparations.

6. Valuable information can be obtained by checking blood penicillin levels and penicillin resistance of the organism.

7. The intermittent intramuscular method of administration of penicillin is the preferred method.

8. It is best that foci of infection should

be removed toward the latter part of treatment when the penicillin blood level is still high.

9. Prophylactically, patients with chronic valvular heart disease or congenital heart disease should be treated with penicillin or a sulfonamide preparation before, during and after removal of foci of infection in order to avoid subacute bacterial endocarditis.

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Epidemiology of Syphilis*

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CASE finding is of first importance in syphilis control. It is the process which must be fulfilled before treatment which leads to the ultimate objective, control, can be effected.

Three factors have been largely responsible for the present emphasis on syphilis case finding: (1) The strengthening of national venereal disease control through the 1938 amendment to the Venereal Disease Control Act, (2) the acceleration of control efforts brought about by the exigencies of the war years and (3) the development of intensive syphilotherapy. This last factor had a dual effect upon case finding. Effective, rapid treatment brought about a realization of the shortcomings of case finding, and at the same time it freed much personnel time heretofore required for the administration of treatment and case holding.

Essentially, there are only three basic methods among many variations of case finding:

Screen Examination. Screen examination is that process whereby physical or laboratory examination for the presence of venereal disease is given an individual because he is a member of a group, all of whom are to be examined because they belong to that group. Prenatal or premarital testing, community-wide blood testing and routine examination among hospital admissions are examples of such groups.

Public Information. Public information includes the planned use of mass informational media, such as newspapers, radio broadcasts, posters and pamphlets, to disseminate among the general population or groups of the population specific facts

regarding the nature of venereal disease. These facts include the means of transmission of venereal disease, symptoms, possible consequences if untreated and the methods and availability of diagnosis and treatment. Discussion meetings, lectures before groups and similar devices for reaching smaller selected groups are also used. The objective of public information is to induce those who suspect infection to seek diagnosis and also to advise how infection may be avoided.

Contact Investigation. This includes all the activities involved in obtaining from each person in whom a diagnosis of venereal disease is established the information necessary to identify and locate persons who may have infected the patient or may have been infected by the patient and in finding these contacts and inducing them to accept examination and, if necessary, treatment. This process is also called "contact tracing," "the direct epidemiologic approach," "shoe leather epidemiology" and sometimes just "epidemiology."

Contact investigation can be used at any time in any area, and through this method syphilis can be found in the early stages even when symptoms are fleeting or unrecognized by the infected person. Theoretically, the investigation of persons known to have been exposed to syphilitic individuals during their infectious period produces the most direct and profitable results of all case finding technics in terms of finding early syphilis. It brings about the examination of contacts when they are infectious or potentially so and thus prevents further spread of the disease. Speed, therefore, is essential in contact investigation if the potentialities of this method are to be realized to the fullest advantage.

* From the Venereal Disease Division, Public Health Service, Federal Security Agency, Bethesda, Md.
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The first step in the investigation process is interviewing the diagnosed patient to obtain identifying information regarding his contacts. The success of the entire process depends upon this interview. In order to break chains of infection new cases of syphilis must be located and brought to treatment before the infection spreads in an ever widening circle.

The source of infection is often emphasized in discussions on contact investigation. Many venereal disease records and reports carry space for insertion of the name of the source. Identifying and locating the so-called source² is important, but overemphasis on this factor has frequently resulted in too little attention being given to the so-called "spread" contacts. Furthermore, it may be impossible and even undesirable to differentiate the source of infection from other contacts. It is probable that latent syphilis would be the diagnosis in a source contact. Those persons to whom the patient may have transmitted the disease are far more likely to be in the open lesion or pre-lesion stage of the disease when examined. Therefore, interviewers should not concentrate their efforts on determining the source of infection but should obtain the names of all persons exposed to the patient within a period when it might reasonably be expected that he was in an infectious period.

Because of the sexual intimacy through which venereal disease is usually acquired, it is sometimes assumed that there may be considerable reluctance on the part of the venereal disease patient to give a physician, health officer or interviewer the information necessary for effective contact investigation. Thus, interviewing for contacts is not emphasized in some clinics and physicians' offices to the same degree that it is for diseases such as smallpox and diphtheria.

In recent years evidence has shown that the venereal disease patient is more willing to cooperate than had been realized. Large groups of patients are willing to give the names of their sex partners, and in many health departments the average is between

three and four contacts per patient. Such success, of course, requires skillful and adequate personnel. Patients will respond to a clear and sympathetic explanation of the need for their cooperation and will demonstrate an active interest in supplying information and assistance. When a friendly, non-censorious approach is used in the interview and when the purpose of the process is discussed with the patient, the average number of contacts obtained is approximately four per patient.

Many states and cities prepare special tabulations on contact investigation which are made available to the Public Health Service for comparative analysis. One of the statistics calculated from these data is the contact index which is the ratio of contacts reported per patient diagnosed. From January, 1944 to December, 1947 the average of all areas for named contacts of primary and secondary syphilis increased from 1.25 per patient to 2.07 per patient. During the six-month period of July to December, 1947 the average number of contacts reported per patient with open lesion syphilis was 2.07. The ratio varied from .43 in one area to 4.14 in another. In a special study conducted in the Venereal Disease Division¹ it was shown that most of the differences between areas in the final accomplishments of contact investigation could be explained by differences in the number of contacts obtained per patient. This factor indicates the importance of good interviewing.

Another study was recently completed on the number of contacts named by 2,000 individual patients with primary and secondary syphilis who gave some contact information.¹ Amazing variation was revealed in the number of contacts named by different individuals. Every patient named at least one contact, and the majority of the patients named two or three contacts. Moreover, 23 per cent of the patients named five or more contacts and 4 per cent named eight or more. It is extremely important that interviewers should be aware that certain patients will name many contacts

and that a minority of patients will name only one contact.

A good interview is the first step in successful contact investigation. Contacts must then be located, examined and placed under treatment if necessary. In general, areas reporting high contact ratios do as well in locating and examining as do areas with low contact ratios. In other words, high contact ratios have not been accomplished by a lowered quality of identifying information or by the addition of persons with little likelihood of being infected. As in interviewing, tact, diplomacy and speed are essential to successful investigation. Speed is doubly important in locating infections before they can be transmitted and in the location of migratory persons. The goal in one area is to have each contact located and examined within four days after being named by the patient.² Proper precautions must of course be taken to re-examine contacts with no obvious signs or symptoms at the first examination, particularly those recent contacts who may be suspected of being in the incubation period of syphilis.

The objective of contact investigation is to prevent the spread of infection, and it is therefore of paramount importance to locate, examine and treat contacts while they are in the open lesion stage. For the period from July to December, 1947 the average number of contacts with primary and secondary syphilis brought to treatment through contact investigation of open lesion syphilis varied from a low of .06 in one state to .29 in another. In certain areas this index has been as high as .47. Because many patients pass into the latent stage before location and examination are accomplished and because lesions are often fleeting or almost non-existent, this lesion to lesion ratio of .47 appears to be a very creditable performance and one which we believe could be attained in any area which intensifies its efforts to do efficient contact investigation.

Perhaps the data from a special experi-

ment in Arkansas² will illustrate what can be done:

Primary and secondary patients	
diagnosed.....	201
Contact index *.....	3.26
Epidemiologic index †.....	1.61
Brought to treatment index ‡.....	0.83
Lesion to lesion index §.....	0.47

It should be noted that each contact brought to treatment with primary or secondary syphilis is in turn included in the enumeration of cases diagnosed and thus presents the opportunity for further contact investigation. There is no duplication of count in the brought to treatment index or lesion to lesion index.³

Contact investigation on syphilis patients treated in public clinics and hospitals does not reach into all chains of infection. The private physician plays a vital rôle in syphilis control as he does in the control of other communicable diseases. Without his cooperation and active interest, the epidemiologic attack on syphilis cannot strike with full force. His friendly, confidential relationship with his patient offers advantages in obtaining information which the physician needs to protect his patient from reinfection and to contribute to the general public health. But physicians are busy men, and often they would welcome competent help in locating the contacts of their patients. This is especially true when contacts have moved to or live in other communities, when identification is difficult or when an infected contact refuses treatment for some reason. The health department can be helpful in many ways, and a close working relationship between the

* Contact index is the ratio of the number of contacts reported to the total number of previously untreated cases in the diagnostic category.

† Epidemiologic index is the ratio of the number of infected persons identified through contact investigation to the total number of patients diagnosed.

‡ Brought to treatment index is the ratio of the number of previously unknown cases found through contact investigation to the total number of patients diagnosed.

§ Lesion to lesion index is the ratio of the number of contacts with primary and secondary syphilis brought to treatment as a result of contact investigation to the number of cases of primary and secondary syphilis diagnosed.

physician and the health department is invaluable to both in their joint effort to control the spread of disease.

With the development of intensive schedules of therapy which lend themselves to out-patient treatment, more and more patients may be handled on an ambulatory basis by private physicians. Physicians have clearly demonstrated their growing interest in all phases of venereal disease control, and it is hoped that the joint efforts

of the physician and the health department in interviewing patients and examining contacts will continue.

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Review

Transmission of Disease by Transfusion of Blood and Plasma*

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RECENT years have brought a dramatic increase in the use of whole blood and blood plasma. As the establishment of blood banks made blood and plasma readily available, it became practicable for the first time to give transfusions

enormous increase in the use of blood and plasma. This is exemplified in Figure 1 which shows the growth of transfusion therapy at the Johns Hopkins Hospital from 1939 to 1946. In the first year after the organization of the blood bank 1,000

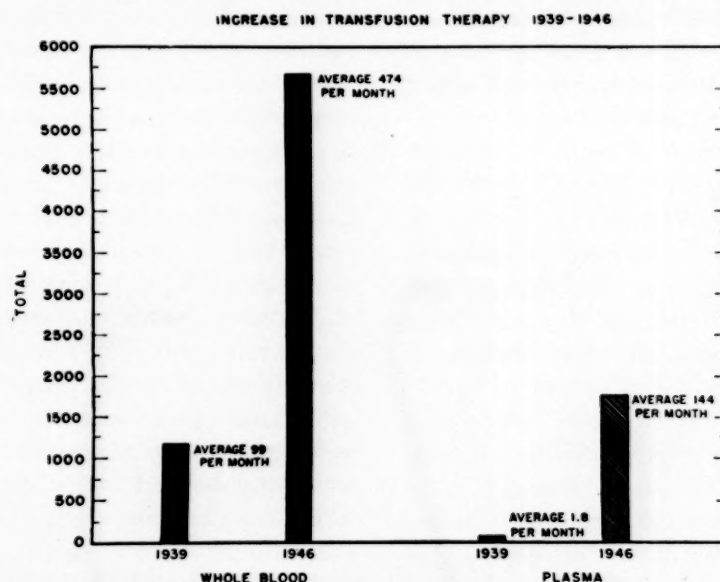


FIG. 1. Transfusion therapy at the Johns Hopkins Hospital in the first year of operation of the blood bank and in 1946.

to large numbers of patients who formerly had barely survived without transfusion, and it was found that five or six or even ten transfusions might save a life while the one or two considered adequate in the past had failed. The extension of the indications for transfusion and the advancement of surgery to permit successful performance of operations of a magnitude previously rarely attempted have combined to produce an

blood transfusions and 22 plasma transfusions were given; in 1946 there were 5,500 blood transfusions and 1,800 plasma transfusions. At present almost every large hospital has a formally organized blood bank of its own and those which do not are beginning to draw upon the recently developed centralized blood banks.

This widespread use of blood is not an unmixed blessing. Blood is a potent thera-

* From the Department of Surgery of the Johns Hopkins University School of Medicine and the Johns Hopkins Hospital, Baltimore, Md. Presented in part in the Forum on Fundamental Surgical Problems, Clinical Congress, American College of Surgeons, New York, September 10, 1947.

peutic agent and a dangerous one. The greatest danger inherent in the blood bank is the relative ease of making clerical errors which may result in the transfusion of incompatible blood. Rigorous application of a careful system of checks will minimize the frequency of such occurrences. A second danger inherent in transfusion therapy under any circumstance is the possibility of transmitting disease. It is obvious that this possibility increases in direct proportion to the increase in frequency of transfusion. It is our purpose to review the pertinent information available concerning the transmission of disease by blood and plasma transfusion, to determine practicable means for the elimination of this hazard and to present available methods which will allow the use of blood drawn from actually or potentially infected donors without risk of infection should transfusion with such blood be necessary or practical.

DISEASES CAPABLE OF TRANSMISSION BY BLOOD TRANSFUSION

The diseases most commonly known to be transmitted by transfusion are syphilis and malaria but during recent years homologous serum hepatitis has become of equal if not greater importance. It is routine practice in transfusion centers to employ precautionary measures to attempt to eliminate the transmission of syphilis and malaria and, to a lesser extent, of transfusion hepatitis. Precautions are required by law in some states. In Massachusetts, for example, the laws governing transfusion therapy read "... No person shall introduce the blood or any unsterilized fraction of the blood or tissue of any donor into the body of any recipient unless said donor has never had syphilis or malaria and is free from any dangerous disease, so far as such freedom from past and present infection can be determined by ... a carefully taken history as to past or present infection with syphilis or malaria ... and a careful physical examination."¹

With the exception of syphilis and malaria, the diseases which have been re-

ported to be transmitted by blood transfusion are few. Baugess² reports two cases and Harrell³ a single case of measles transmitted to infants, the donors being in the incubation period at the time of bleeding. Robertson⁴ and J. R. Blalock⁵ each report a case of smallpox transmitted by transfusion. Three cases of transfusion typhus^{6,7,8} have been reported from Europe. Levick⁹ reports from England a single case of influenza transmitted by transfusion. Hendrick¹⁰ in her review of the subject cites three cases of tuberculosis reported from Europe by Opitz in 1925. Relapsing fever, due to the *Spirillum recurrentis* of Obermeier, developed following transfusion in six patients reported by Wang and Lee.¹¹ Beckman¹² reports a case of fatal encephalitis following transfusion of blood taken from a donor in whom chickenpox developed three days after bleeding. A single case has been reported¹³ of gonorrheal arthritis appearing in an eight months old male infant after two transfusions from his gonorrheal mother. A case of *B. Suipestifer* septicemia has been observed in the Venereal Disease Clinic of the Johns Hopkins Hospital following transfer of therapeutic malaria.¹⁴ The possibility of transmitting the above diseases is slight and it is believed that a reasonably complete and accurate history and an adequate physical examination should disclose donors suffering from these diseases or still in the infective prodromal stage.

HOMOLOGOUS SERUM HEPATITIS

Although jaundice following the injection of human tissue extracts was recognized and reported as early as 1885 by Lürman,¹⁵ it is only within recent years that homologous serum hepatitis has attracted widespread attention. Findlay and MacCallum¹⁶ in 1937 reported its occurrence after vaccination against yellow fever, and McNalty¹⁷ in 1938 discussed its appearance following the use of pooled measles convalescent serum. With the outbreak of the recent war when large numbers of troops were vaccinated against yellow fever, homologous serum hepatitis became recognized as a matter of

universal concern. Between January 1, 1942, and July 1, 1942, over 28,000 cases of hepatitis resulting in sixty-two deaths had occurred subsequent to yellow fever vaccination of about $2\frac{1}{2}$ million persons.¹⁸ Subsequent investigations showed that the icterogenic agent was contained in the human serum which had been used as a vehicle and stabilizer for the immunizing agent.^{19,20} Since that time similar cases of hepatitis and jaundice have been recognized following the administration of whole blood and more particularly of plasma. Reports from civilian hospitals are few but significant.^{21,22} Six cases of jaundice following transfusion therapy and twice this number following therapeutic malaria transfer, all presumably cases of homologous serum hepatitis, have been observed at the Johns Hopkins Hospital. Recent reports of military experiences have indicated that in battle casualties this disease was a rather frequent occurrence attendant upon the use of large quantities of pooled plasma.²³ The disease is a serious one and its development following transfusion therapy must be regarded as a grave complication.

The exact incidence of homologous serum hepatitis following transfusion therapy is not known. Spurling, Shone and Vaughn in England²² found an incidence of 7.3 per cent among 1,054 recipients followed five months or longer after receiving pooled plasma or serum. They were able to discover only six doubtful cases of homologous serum hepatitis in 891 recipients of whole blood transfusions taken from single donors. Grossman and Saward²¹ report an incidence of 1.6 per cent in recipients of 501 transfusions of commercial pooled plasma. The incidence among war casualties who received transfusion therapy was about 2 to 3 per cent²⁴ and this figure seems to represent a fair average. Such an incidence assumes an even more disturbing significance when it is realized that this disease carries with it a fatality rate of 2 to 3 per cent.²⁴ This is ten times higher than that of infectious hepatitis which it so closely resembles.

The exact relationship of homologous serum hepatitis and infectious hepatitis has not been determined. The etiologic agents do not seem to be identical, certain significant differences having been definitely established. The properties of the etiologic agent of each of these diseases suggest that they are viruses. Neither agent, however, has been visualized by the electron microscope^{25,26} nor have attempts to cultivate them on ordinary or chick embryo media been successful.²⁰ No specific serologic test has as yet been found.^{20,27,28} The most important hindrance to the study of these diseases has been the lack of any susceptible laboratory animal.^{20,29,30,31,32} Transmission experiments have, therefore, been limited to human volunteers.

There are certain similarities between the causative agents of the two diseases. Both pass through bacteria-trapping filters.³¹⁻³⁴ Both survive heating at 56°C. for thirty minutes.³⁰ Both survive freezing for a period of years³⁵ and no diminution of virulence has been noted after storage at 4°C. for periods up to one year.³² Storage at room temperature for one year does not seem to destroy the viruses.³⁶ Both survive exposure to the ordinary bactericidal agents for long periods of time.^{34,37} The disease processes are clinically similar though not identical and the pathologic lesions are indistinguishable.³⁸

A distinction between the two diseases was suggested by the rather constant difference in the incubation periods, infectious hepatitis usually appearing in less than forty days after exposure, while homologous serum hepatitis becomes manifest from fifty-five to one hundred thirty-five days after transfusion. The onset of infectious hepatitis is often accompanied by high fever whereas homologous serum jaundice produces relatively little fever.³⁵ Differences in the method of transmission are significant. The virus of infectious hepatitis may be recovered from the feces of infected patients and the disease is readily produced by oronasal inoculation with material from this source.^{31,33,35,41,42,43,48} Epidemiologic observations lend strong support to the theory

of alimentary transmission. Transmission of infectious hepatitis by the parenteral injection of blood products has only occasionally been successful and does not seem to be the natural method of infection.^{30,39,40,44,45}

The virus of homologous serum hepatitis, however, routinely produces a typical infection when injected parenterally, and attempts to produce the disease by oral inoculation with blood or blood products have been almost uniformly unsuccessful.^{35,41,43} This agent has not been recovered from the feces of an infected patient.^{35,45,46} The transmission of this disease is apparently accomplished solely by artificial means, that is, by parenteral injection of blood or blood products. Recent evidence indicates that the disease may be transmitted by contaminated syringes or needles.^{47,49,50,51} Each of these diseases produces a definite long-lasting homologous immunity.^{32,35,42,44,52,53} No cross immunity has been demonstrated^{35,44,53} suggesting at least a definite antigenic difference between the two viruses. From the fact that many persons over thirty years of age show a definite resistance to the virus of infectious hepatitis,^{42,54} it has been inferred that many subclinical infections occur with resultant complete or partial immunity. This may be true for homologous serum hepatitis since it is known that some recipients of icterogenic material do not develop clinically recognizable hepatitis. The fatality rate of the two diseases is strikingly different, that of homologous serum hepatitis being ten times as great as that of infectious hepatitis.²⁴ In view of these dissimilarities it would seem most likely that the etiologic agents of these diseases are similar but not identical.

In any case, there can be little doubt that the increased incidence of serum hepatitis among the armed forces and civilians is due to the increased use of pooled plasma. The amount of icterogenic plasma required to contaminate a pool is extremely small, as little as 0.01 cc. being sufficient to transmit the disease.³¹ If but one donor of a 5,000 unit pool were infected, each plasma unit from this pool would still contain five times

the amount of icterogenic plasma necessary to transmit the disease.

PREVENTION OF HOMOLOGOUS SERUM HEPATITIS

Our present methods for preventing homologous serum hepatitis are grossly inadequate. The following, however, are worthy of consideration:

The Control of Donors. Although it has never been proven that carriers of homologous serum hepatitis exist, most blood banks exclude donors with a history of jaundice. While this measure is probably justified because of the possibility that a carrier state exists, it is somewhat illogical since donors in the presymptomatic stage of the disease are presumably the source of greatest danger. The icterogenic agent has been demonstrated in the blood stream of an experimentally inoculated human volunteer as long as eighty-seven days prior to the onset of clinical hepatitis and is present in the blood until the onset of clinical symptoms.^{36,41} Although there is not as yet sufficient evidence available to justify definite conclusions, it seems that the virus probably disappears from the blood soon after the onset of jaundice. Data concerning the presence of the virus in the blood following recovery from the disease are not available. We cannot expect to reduce significantly the number of cases of homologous serum hepatitis by elimination of donors.

Reduction in the Size of Pools. Since a single unit of icterogenic plasma will contaminate a very large pool, it would seem logical to eliminate the pooling system and to use only individual units of plasma made from the blood of a single donor. Such a plan would reduce the number of people exposed to the infected blood. On the other hand, there is some danger of incompatibility reactions in the use of unpooled plasma, and such a policy would reduce the production of plasma to a much less efficient process and thereby decrease the ready availability of plasma created by the use of large scale production methods. A compromise method would be the use of smaller

plasma pools using blood drawn from six to eight donors, thereby reducing the number of recipients exposed.

The Use of Plasma Fractions. When the subject of homologous serum hepatitis was first brought into prominence it was noted that no cases were observed following the administration of gamma globulin.³⁵ This suggested that perhaps this fraction of the plasma might contain some substance protective against the icterogenic agent. Data on this aspect of the problem are inconclusive^{23,55,56,57,58} but the method seems to offer little promise for preventing transfusion hepatitis. Similarly we have found no reported cases of transfusion hepatitis following the use of human serum albumin. This would suggest that the agent is destroyed in the process of fractionation.

Ultraviolet Irradiation. The studies of Oliphant³² suggest that the virus of homologous serum hepatitis may be inactivated by exposure to ultraviolet irradiation. Evidence for this is not conclusive. Final application of this method must await further studies of the effect on the virus. The recent studies of Wolf⁵⁹ and his co-workers indicate that plasma irradiated by the method of Oppenheimer and Levinson⁶⁰ is not altered chemically and may be given to human beings without ill effect. The technical difficulties of irradiating plasma in large quantities constitute a considerable obstacle which has not as yet been overcome.

Fifth, it may be possible to heat plasma to a temperature lethal to the virus without rendering the plasma unfit for parenteral use. Lastly, the capacitron⁶¹ offers another avenue of investigation.

TRANSFUSION SYPHILIS

The first recorded case of transfusion syphilis was reported by Fordyce in 1915⁶² and we have been able to collect almost 100 cases cited in the literature since that time. Since this number probably represents but a small fraction of the number of cases which have gone unrecognized or unreported, the importance of this complication of transfusion therapy cannot be

ignored. Twelve cases of transfusion syphilis are known to have occurred in the Johns Hopkins Hospital.⁶³ None of these, however, has occurred since the organization of the blood bank in 1939.

Syphilis is primarily of interest in blood bank administration from the point of view

TABLE I
INCIDENCE OF POSITIVE SEROLOGIC TESTS FOR SYPHILIS IN
BLOOD DONORS AT THE JOHNS HOPKINS HOSPITAL
BLOOD BANK—1946

	Total Donors	S.T.S. Positive Donors	Per cent
White.....	4212	50	1.2
Colored.....	3295	437	13.3
Total.....	7507	487	6.5

of the patient's welfare and the prevention of transmission of the disease to recipients by way of transfusion. Of great practical interest to the blood bank, however, is the fact that large quantities of blood must be discarded because of positive serologic tests for syphilis. Table I shows the incidence of positive serologic tests for syphilis among donors bled in the blood bank of the Johns Hopkins Hospital during 1946. It must also be remembered that all donors with a history of syphilis or of antisyphilitic therapy were rejected and therefore are not included in these figures. MacNamara⁶⁴ has shown that syphilis is not transmitted by transfusion of blood drawn from donors with tertiary syphilis. There is also reason to believe that blood drawn from syphilitic patients other than those in the late stages can be used without infection. If such blood could in some manner be made available for use a very considerable waste would be prevented.

Transfusion syphilis differs from the disease as contracted by genital or extra-genital inoculation only in the absence of the chancre. The first manifestation of the disease is almost invariably the development of secondary lesions although in a few patients this phase has been absent or so insignificant as to escape notice and the

late manifestations have been the presenting symptoms. Klauder and Butterworth⁶⁵ in 1937 analyzed thirty reported cases of transfusion syphilis and found that the incubation period varied from four to sixteen weeks, the majority of the patients showing secondary lesions between the eighth and the tenth weeks. This observation corresponds exactly to the incubation period of the disease as contracted by the usual genital or extragenital invasion, the chancre appearing in about three weeks and the secondary lesions developing about six weeks after the appearance of the chancre. As far as is known, there is no difference in the prognosis of transfusion and of natural syphilis and there is no recognized difference in the response to therapy.

METHODS FOR THE PREVENTION OF TRANSFUSION SYPHILIS

Prior to the organization of blood banks it often happened that no test for syphilis in the donor was performed before transfusion. This was due either to lack of technical facilities or to the emergency nature of the transfusion. Such was the case in 75 per cent of the forty-one cases of transfusion syphilis collected by Eichenlaub and Stolar⁶⁶ in 1939. Since the establishment of blood banks we no longer face these problems. With a large store on hand at all times blood is routinely kept long enough to allow serologic tests for syphilis to be performed before the blood is used. In the cases collected by Eichenlaub and Stolar⁶⁶ 39 per cent of the donors had, or presumably would have had, a negative serologic test for syphilis immediately before giving blood since they were in the incubation period of the disease before the appearance of the chancre. In addition, as seen in Table II,⁶⁷ in every stage of syphilis a certain fraction of the patients will have negative serologic tests and except in secondary syphilis the fraction is substantial. In the group of infective though seronegative donors lies the hazard of transfusion syphilis. It seems obvious that despite faithful performance

of the most accurate serologic tests available we may still encounter cases of transfusion syphilis. What further measures are available to us to prevent such an accident?

Mütermilch⁶⁸ in 1932 attempted to prevent infection by adding cyanide of mercury

TABLE II
INCIDENCE OF NEGATIVE SEROLOGIC TESTS IN UNTREATED
SYPHILITICS

Type	Seronegative Per cent
Primary.....	30
Secondary.....	0.9
Latent.....	0 (serol. diag.)
Late (except neurological).....	18.8
Diffuse meningo-vascular.....	10.1
Paresis.....	11.3
Tabes.....	18.1

to infected blood in a concentration of 1 mg. per ml. The toxicity of this drug and the large amounts required render this method unsafe. Furthermore, Gougerot and his co-workers⁶⁹ report two cases and Hudelo⁷⁰ a third case of transfusion syphilis which developed in spite of the addition of 5 mg. of cyanide of mercury to 10 ml. of serum which was injected intravenously. This method cannot be considered practical or safe.

Kast, Peterson and Kolmer⁷¹ in 1939 advocated the addition of neoarsphenamine to whole citrated blood to prevent transfusion syphilis, reporting their well controlled *in vitro* and rabbit inoculation experiments which demonstrated the high treponemical effects of arsphenamine and neoarsphenamine. They found both drugs completely treponemical in a dilution of 1:10,000. If such a concentration were used with the usual 500 ml. transfusion, the recipient would receive 50 mg. of the drug or approximately one-fifteenth of the average single therapeutic dose. In the concentration recommended, 1:10,000, the drug is not hemolytic and does not agglutinate the red cells.⁷¹ Kast et al. also reported the administration of transfusions containing this concentration of neoarsphenamine or arsphenamine to eight persons with no evidence of toxicity. Occasionally the use of such blood might be contraindicated and in any case one would have to accept

the risk of a small but definite incidence of arsenical sensitivity reactions.

In 1941 Turner and Diseker⁷² and Bloch⁷³ independently demonstrated that whole blood inoculated with active treponemes loses its infectivity before ninety-six hours of storage at 4°C., and in 1942 Ravitch and Chambers⁷⁴ showed that plasma inoculated with active treponemes and then frozen lost its infectivity after less than forty-eight hours in the frozen state. This experimental work suggests a practical method of preventing transfusion syphilis. Routine storage of all blood in the refrigerator at 4°C. for four days would prevent any recipient from acquiring syphilis even if serologic tests were not made. Similarly, known syphilitic blood may be used for the preparation of plasma with no danger of transmitting syphilis since plasma is routinely kept frozen at least a week before use while cultures are being made. Prior to the organization of the blood bank twelve cases of transfusion syphilis were observed in the Johns Hopkins Hospital. Since 1939, however, with over 40,000 blood and plasma transfusions, no cases have been recognized. Considering the figures for the incidence of infectious seronegative donors (Table II) it must be concluded that simple storage at 4°C. must have prevented a considerable number of cases of transfusion syphilis. No attempt has been made to require four-day storage of all blood and in view of the absence of cases of transfusion syphilis such a policy would not seem to be indicated. If, however, in a given center the proportion of seropositive donors were greater or the incidence of transfusion syphilis appreciable or if, for some reason, one desired to use seropositive blood, adoption of such a plan would be advisable. Addition of one of the arsenicals provides a possible means of attack on the problem.

The use of seropositive blood for the production of plasma offers a method for eliminating the waste incurred in rejecting donors with a history of syphilis or anti-syphilitic therapy and that incurred in discarding all seropositive blood. Trans-

fusion with such plasma will temporarily render positive the recipient's serologic test for syphilis. This problem is under study by one of us (M. M. R. with T. Farmer and B. Davis)⁸⁷ and results indicate that the serologic tests for syphilis revert to negative within one to two weeks.

TRANSFUSION MALARIA

The possibility of transmitting malaria by transfusion has long been known. The first case of accidental transmission recorded is that of Woolsey⁷⁵ who in 1911 reported the development of malaria in a recipient after a direct artery-to-vein transfusion. Since that time there have been sixty reports of transfusion malaria occurring in non-endemic areas, twenty of these having been reported during the past eight years. Malaria is endemic in only a very small section of the United States. This area has constantly shrunk and the small group of persons in this country harboring active or latent malarial infections has gradually diminished. Since World War II, however, the situation has changed. With the return to the United States of the large numbers of servicemen who served in malarial zones, the number of malarial infections, both latent and active, in all parts of the United States has increased greatly. The geographic and epidemiologic factors are such that an increase in mosquito-borne malaria is not expected in most regions of the United States. However, the increase in malaria in our population and the concomitant increase in transfusion therapy will almost surely bring an increase in transfusion malaria unless preventive measures are taken. Thus, malaria now presents a considerable hazard in transfusion therapy and has become a point of vital interest to our rapidly increasing and expanding blood banks.

Malaria inoculata does not differ significantly in its characteristics from naturally incurred malaria. It has been noted⁷⁶ that in quartan malaria the incubation period, dated from the onset of fever, is eight days or less when the disease is contracted

artificially (trophozoite) but is about thirteen and a half days when acquired naturally (sporozoite). The duration of the initial attack, however, is not significantly different, the characteristics of the attacks and the paroxysms are the same and the recurrence rate is approximately the same. Except for the length of the incubation period these observations hold equally for the other types of malaria.

PREVENTION OF TRANSFUSION MALARIA

The most obvious and most frequently advocated method for the prevention of transfusion malaria is the rigid questioning of donors concerning a past history of clinical malaria or their past residence in an area in which malaria is endemic, and the rejection of all donors who give a positive history of either. The task of obtaining an accurate and reliable history may be extremely difficult. In this connection we must appreciate the remarkably long periods of latency which are compatible with a still active and virulent malarial infection capable of being transmitted by blood transfusion. Jankleson⁷⁷ reports a case of transfusion malaria in which the donor's last possible exposure to infection had occurred forty years before and there are several instances reported with a latent period of twenty-five years. Reliance upon history to rule out malarial donors will lower the incidence of transfusion malaria but will not prevent it. In addition, this plan has the obvious disadvantage of reducing the number of donors available for bleeding. If we adopt the safer policy of rejecting all donors who have at any time lived in a malarial area the number of acceptable donors becomes even more limited, especially in view of the large number of young men recently returned from service in endemic zones. In the regions of the United States in which malaria is endemic such a policy would be almost prohibitive. Examination of the known facts concerning the transmission of malaria would suggest that a policy of wholesale rejection of donors is not necessary.

Ackerman and Filatov⁷⁸ reported the most thorough investigation of this problem in 1934 when they studied the survival of tertian plasmodia in blood stored for varying lengths of time under conditions simulating those now found in blood banks. Survival was tested by smear and by inoculation of patients suffering from "... central nervous system diseases in which malarial therapy was indicated." Their experiments showed that tertian plasmodia did not survive after ninety-six hours of storage. Clinical experience supports this conclusion. In none of the reported cases of tertian transfusion malaria had the blood been stored as long as four days. The same conclusions do not seem to stand without reservation for the other forms of malaria. Two cases of quartan malaria following transfusion with five-day old bank blood are reported by McClure and Lam⁷⁹ and a third case of transfusion quartan malaria following transfusion with blood stored for eight days is cited by Antschelewitsch.⁸⁰ There are two cases of transfusion malaria recorded in the histories of the Johns Hopkins Hospital. The first was included in a report by F. Howell Wright in 1938⁸¹ and occurred in a nine-month infant who received a transfusion of fresh citrated blood from his father who had had clinical malaria twelve years previously but had been asymptomatic since. The parasites in the baby's blood were demonstrated to be quartan. No parasites could be demonstrated in the blood of the father. The second case occurred in 1946 in a sixteen year old boy with congenital hemolytic jaundice who was brought into the hospital for splenectomy. On the day of operation he received two transfusions of 500 cc. of whole citrated blood. Recovery was uneventful and he was discharged from the hospital. He was re-admitted six weeks later with a history of sudden onset of severe chills and high fever beginning four weeks after discharge and six weeks after his two blood transfusions. He had been having chills regularly every seventy-two hours during the two weeks prior to ad-

mission. Quartan parasites were readily demonstrated in his blood and his paroxysms disappeared immediately upon the institution of atabrine therapy.

The donors of the transfusions which the patient had received were examined but neither could be proved to have a malarial infection. The first donor was a forty-three year old white male of Sicilian birth who migrated to this country at the age of seven years. He gave no history of malaria. The second donor was a twenty-two year old white male who had been discharged from the Army a short time prior to donating blood, having served in Africa and the South Pacific and having had a febrile illness in the latter area which was not proved to be malaria. Neither donor had a palpable spleen and smears taken after subcutaneous injection of adrenalin were negative for parasites. The patient was born in New York, moved to Maryland at the age of one and one-half years and had never been exposed to malaria. He gave no history of any previous illness suggesting malaria. In view of these facts it is believed that despite the failure to demonstrate parasites in the blood of the donors it may be assumed that this represents a case of transfusion malaria. As these transfusions were given after the blood had been stored for periods of forty-eight and ninety-six hours, respectively, they throw no new light on the length of survival of quartan plasmodia when stored under blood bank conditions. Until further experimental work is done with quartan and malignant tertian parasites it would seem inadvisable to depend on storage alone to prevent malaria inoculata.

The second obvious method of rendering blood non-infectious which is actually or potentially infected is the introduction of a plasmodicide into the blood. Such attempts have thus far been unsuccessful. Quinine in concentrations up to 1:1,000 has no effect⁷⁸ nor have any of the other antimalarial drugs proved more effective.⁸²

Benign tertian or quartan malaria inoculata has long been recognized to be a rela-

tively mild form of malaria, particularly sensitive to antimalarial therapy. Thoroughman⁸³ in Soochow, China, attempted to solve the problem from this point of attack. In that highly endemic area 176 transfusions from unselected donors produced transfusion malaria in 53 per cent of the recipients. In his experiments he considered all donors to be potentially infected and accordingly, in a series of thirty-four transfusions, gave all recipients 0.9 Gm. of quinine per day for the three days following transfusion. No infections occurred although normally fifteen persons would have been expected to develop clinical malaria. A similar plan was proposed by R. R. Officer⁸⁴ of Australia who inoculated five subjects with blood drawn from donors with proved benign tertian malaria. He protected the recipients by simultaneously beginning a course of quinine-atabrine-plasmochin therapy and again no infections were observed. These antimalarial drugs may probably be advantageously supplanted by the newer drugs, chloroquine and chlorguanide. Obviously such methods are not meant for general use in non-endemic areas. They do, however, present a feasible method for the prevention of transfusion malaria in instances in which transfusion with potentially infected blood is a necessity regardless of the risk of infection. Such a situation might arise in military medical practice or in civilian practice in areas of high endemicity. In tropical regions and to a lesser extent in endemic areas of the United States such a program might be advantageous.

As yet no method is known which will allow the safe use of fresh whole blood drawn from donors with actual or potential malarial infection. However, it is not necessary to refuse all donors who give a history of malaria or of residence in an endemic area. The plan now in use in the blood bank at the Johns Hopkins Hospital is supported by the work of Lozner and Newhouser⁸⁵ who showed that plasma prepared from blood proved to be infected with active quartan or falciparum parasites could be given safely without risk of infection. They

prepared plasma from infected blood and stored it at -20°C . for periods varying from five to thirty-four days. In twenty transfusions using this plasma no cases of malaria inoculated were observed. Since plasma is necessarily kept for at least seven days while cultures are being made, the safety factor is more than adequate. It is significant that although storage at -20°C . kills the plasmodia, freezing at -72°C . is used as the method of preservation of plasmodia, the parasites retaining their virulence for long periods of time at this temperature.⁸⁶ The same is, of course, true of *Treponema pallidum*. An additional factor of safety lies in the obvious fact that the parasites, which are for the most part within the red cells, are almost entirely removed in the preparation of plasma.

It would seem then that at the present time there is no method which can be adopted by blood banks which will safely permit the use of whole blood potentially or actually infected with malaria except the concomitant use of antimalarial therapy for the recipient. It is no longer necessary, however, to reject donors giving a positive history of malaria or of exposure to malaria. Frozen plasma prepared from the blood of suspected donors can be used with safety.

SUMMARY

1. The possibility of transmission of disease through transfusion has increased in proportion to the increase in transfusion therapy. The diseases which must be considered most seriously are homologous serum hepatitis, syphilis and malaria.

2. The incidence of homologous serum hepatitis has been greatly increased by the use of pooled plasma. Reducing the size of plasma pools will limit the incidence of the disease. Fractionation of plasma is one avenue of approach to the problem. Physical methods may inactivate the virus without injuring the plasma.

3. In spite of careful selection of donors a low but definite incidence of transfusion syphilis may be expected. Blood containing active treponemes may be rendered safe

for use either by adding an arsenical in a dilute concentration or by storage at 4°C . for ninety-six hours. Infected blood may also be utilized by converting it to plasma and storing it at -20°C . for forty-eight hours. Recipients of such plasma will develop positive serologic tests for syphilis for from one to two weeks. Such a program would prevent the waste of large quantities of blood now discarded because of positive serologic tests for syphilis.

4. No method has been found which will allow blood banks to utilize safely whole blood infected with malaria. If under some circumstances it should be necessary to employ actually or potentially infected blood, transmission can be prevented by the concurrent institution of antimalarial therapy. Plasma made from infected blood and stored at -20°C . for five days can be used without danger. Persons with a past history of malaria or of exposure to malaria may, therefore, be accepted as donors.

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Seminars on Congestive Failure

Mechanisms of Salt and Water Retention in Heart Failure*

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DURING the development of chronic congestive heart failure, salt and water are retained. The cause of this retention has been the subject of a lively recent controversy. The final answer is not yet clear but a more rational solution to certain phases of the problem has been discovered.

The concept of fluid being forced into the tissues by an increased venous pressure seems no longer tenable. Such a situation should result in hemoconcentration whereas chronic congestive heart failure is associated with hemodilution.^{1,2} Furthermore, any *sustained* elevation of venous pressure must be balanced by a supporting increase in tissue pressure³ and this is not easily explained by the theory of brief reduction in cardiac output. Altschule⁴ found the venous pressure to be between 8 and 71 cm. saline in seven of fifteen patients with cardiac edema whereas normal subjects showed pressures below 10. We have made similar observations using direct atrial pressure readings in edematous subjects⁵ so that the objections often raised to measurements using peripheral veins would seem to be answered. Venous pressures as high as 50 cm. saline, without demonstrable edema, have been recorded by Burch and Ray^{6a} in patients following ligation of the inferior vena cava. In addition to this several cardiac patients have been reported with venous pressures as high as 16 to 31 cm. water without visible edema.^{6b} We have seen one individual with constrictive pericarditis and one with chronic heart failure with atrial

pressures of 23 cm. and 27 cm., respectively; the first patient never had edema and the second was edema-free at the time of the measurement. Thus it is evident that there is little correlation between the presence of edema and the level of venous pressure. Starr⁷ measured the "static" venous pressure in patients with heart failure immediately after death and found it elevated even after the heart had stopped beating. He also showed⁸ in dogs that almost complete destruction of the right ventricle with a cautery resulted in no elevation of venous pressure. These experiments suggest that right ventricular failure *per se* has little to do with elevated venous pressure. The second of the two intimates that the left ventricle may be capable of carrying practically all of the circulatory load in dogs at rest. In mentioning "right ventricular failure" one must bear in mind that the left ventricle can pump only as much blood as passes through the right ventricle, so that when the right ventricle "fails" the left must also fail. Landis⁹ demonstrated that fluid accumulated in the tissues with venous pressures of 15 to 20 cm. water. However, he used a tourniquet applied above the elbow which would also produce lymphatic obstruction.

If interference with lymph flow were implicated, one would expect a relatively high protein content of the edema fluid since one of the functions of the lymph vessels is to return protein to the blood stream. Stead and Warren¹⁰ found the average protein content of cardiac edema

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fluid to be quite low (average 0.24 Gm. per cent) in fourteen patients. In our opinion this also indicates that capillary permeability is not appreciably increased as the relative proportion of protein to water should be greater in subjects with increased capillary permeability, although some disagree.¹¹ Stead and Warren¹² studied two patients with chronic congestive heart failure who had been freed of edema by the use of sodium restriction and mercurial diuretics. These patients had exhibited consistent signs of heart failure over a long period of time, had regular rhythm and both had cardiac outputs well below average.¹³ As salt was added to the diet in amounts easily eliminated by normal subjects, the patients had an increase in weight and blood volume which definitely preceded the rise in venous pressure. Harrison, Reichsman and Grant¹⁴ gave evidence which seemed at variance with these findings. Patients with auricular fibrillation who were fully digitalized were taken off digitalis and allowed to fibrillate at a rapid rate. In their patients a rise in venous pressure preceded the weight gain. However, these authors most likely were dealing with patients with a changing cardiac output. An individual with a stabbed heart and pericardial tamponade with a sudden fall in cardiac output may get a rise in venous pressure and hematocrit without change in blood volume (except sometimes a slight decrease associated with the venous pressure rise) supposedly due to capillary or venous constriction. Arteriolar constriction *per se* would hardly account for this change. Cooper, Stead and Warren demonstrated this phenomenon in dogs.¹⁵ A similar mechanism was probably involved in the experiments of Harrison, Reichsman and Grant. Lyons¹⁶ gave large amounts of sodium salts to normal individuals. The weight and blood volume rose simultaneously and finally the venous pressure became elevated. This indicates that when the body receives more salt than the kidney can excrete, salt and water are retained and the venous pressure rises secondarily.

There can be no question that, in the last analysis, edema of heart failure is the result of failure of the kidney to excrete salt and water normally. That the primary difficulty is with salt and not with water has been demonstrated by many observers.¹⁷⁻²⁰ The sodium ion and not the chloride ion is the one implicated in edema, as sodium bicarbonate produces edema and ammonium chloride causes diuresis.²¹

Futcher and Schroeder²² and Reaser and Burch²³ have demonstrated that the kidney in chronic heart failure is unable to excrete sodium normally. Seymour et al.,² in an effort to explain this, showed a decreased renal plasma flow (PSP clearance) and filtration rate (inulin clearance) in patients with heart failure, with return toward normal after digitalization. They attributed these changes to the elevated venous pressure as the fall in venous pressure with digitalis was accompanied by improvement in renal function. It should be pointed out, however, that they were dealing with a third variable—the cardiac output—which they showed to increase with digitalis. Much confusion about cardiac output in heart failure has arisen from a failure to recognize that the resting cardiac outputs which have been measured in the past are of significance only in subjects who have heart failure at rest. In these individuals the cardiac output is consistently low.

Studies were made in our laboratory on patients with both "acute" and "chronic" heart failure using hippurate and inulin clearances,^{24,25} cardiac outputs employing the direct Fick principle^{26,27} and some atrial pressures measured through a catheter lying in the right atrium.²⁸ The "chronic" patients were those who had fixed heart failure at bed rest. This usually does not change when the patient is relieved of his signs of congestive failure by the only means possible—either rigid sodium restriction or the use of mercurial diuretics. The patients with so-called "acute" failure have normal resting cardiac outputs but are able to increase the cardiac output very little with exercise.²⁹ In other words, they are the

patients with a low cardiac reserve. In the group with a low cardiac output the renal plasma flow was reduced from one-third to one-sixth normal, whereas the cardiac output was seldom less than one-half normal. Thus the kidney was receiving on an average of 8 to 10 per cent of the cardiac output instead of its usual 20 to 25 per cent. This suggests a shunt away from the kidney produced either by relative intrinsic vasoconstriction in the kidney or by relative vasodilatation in other parts of the body. Also, the filtration rate remained within normal limits or slightly below until the renal plasma flow was about 200 cc. per minute or less (normal 600 to 700 cc./min.). This was probably accomplished by a rise in filtration pressure produced by constriction of the efferent arteriole of the glomerulus. Thus the fraction of renal plasma flow filtered (filtration fraction) was as high as 40 to 60 per cent, the normal being about 20 per cent.

By dividing patients into "chronic" and "acute" groups according to whether or not they required mercurial diuretics for compensation and by studying their inulin clearances, the "critical" filtration rate for sodium retention was found to be about 70 cc. per minute.³⁰ However, these patients were not at absolute bed rest and some of them might not have required mercurials if they had been. Therefore, it is possible that the level should be somewhat lower. There was a distinct correlation between the severity of symptoms and the level of filtration rate. This does not prove that the low filtration rate is the cause of the sodium retention as each might be an unrelated phenomenon set in motion by a common cause.

It has been shown that renin produces efferent arteriolar constriction³¹ and it is well known that renin production is increased in subjects with a low cardiac output. Renin is not demonstrable in blood coming from the kidney of normal individuals but it was demonstrated in the renal vein blood of eight of ten patients with heart failure. No renin was found in the arte-

rial blood of patients with heart disease.³² However, the bio-assay technic employed dogs. While this is adequate to determine an increased concentration of renin, a more sensitive method is needed to decide whether there is an absolute increase or simply the same amount secreted into the reduced amount of blood flowing through the kidney. If renin production is increased, it offers a possible explanation for the mechanism of arteriolar constriction and perhaps venoconstriction seen in heart failure, as renin is known to produce such effects.³³

We also found a decreased excretion of sodium in patients with heart failure which was roughly proportional to the decrease in filtration rate and we explained the sodium retention on this basis. We believed at the time that the tubules continued to reabsorb sodium because of their "fundamental sodium-conserving function," although it was admitted that other causes might exist.²⁸ Mokotoff, Ross and Leiter³⁴ showed that sodium reabsorption paralleled sodium filtration in heart failure and gave a mathematical formula, reabsorption of sodium = filtration rate x plasma sodium, representing this relation. This does not reveal the cause of sodium retention in heart failure, as sodium filtration and sodium reabsorption are such large quantities as compared with sodium excretion that the latter could be multiplied several times without affecting the formula appreciably. One is forced to conclude, as Newburgh and Leaf³⁵ have done, that an evaluation of the role of the filtration rate in sodium excretion cannot be made directly because sodium excretion is so small and the errors in the inulin determination of filtration rate are so large. Indirect evidence is given below.

To determine whether the same principle of low filtration rate applied to patients with a normal resting circulation, it was necessary to study them in the exercising state since their failure occurs only under such conditions. We²⁹ found that six of ten cardiac subjects showed a fall in filtration rate to the "critical" level of 70 cc./minute

when they performed mild exercise roughly equivalent to walking leisurely on level ground. Sodium excretion was markedly diminished in two cardiac subjects who had a fall in filtration rate with exercise and not in a cardiac patient whose filtration rate

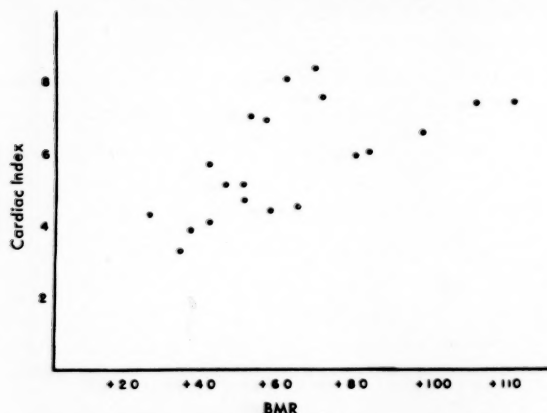


FIG. 1. Note that the cardiac index increased in direct proportion to the BMR. (Courtesy of Dr. E. S. Brannon.)

did not decrease with exercise. This seemed to fall in line with our hypothesis. But Kattus et al.³⁶ demonstrated a fall in sodium excretion with exercise in normal subjects who had no decrease in filtration rate although they did find a somewhat greater decrease in sodium excretion in their cardiac subjects who had a diminished filtration rate with exercise. It appears that there may be a mechanism for sodium retention during exercise which is partially if not entirely independent of the filtration rate. As already pointed out, the errors in inulin clearance are great and Kattus'³⁶ studies can be evaluated better when the data are published in detail.

The foregoing experiments do not account for the patients who have heart failure with high resting cardiac outputs such as those with anemia, thyrotoxicosis and beri-beri. Heart failure is rare in resting anemic subjects with normal kidneys and no heart disease. Bradley³⁷ found that anemia results in a low renal blood flow. We⁵ found that the renal blood flow is reduced but the renal plasma flow is relatively normal except in very severe anemia because of the relatively high proportion of plasma in anemic blood. The filtration rate

is unaffected. In thyrotoxicosis the cardiac output varies directly with the basal metabolic rate. (Fig. 1.) All those with heart failure have a high cardiac output. Most of those who have congestive heart failure exhibit slight increases in the cardiac output

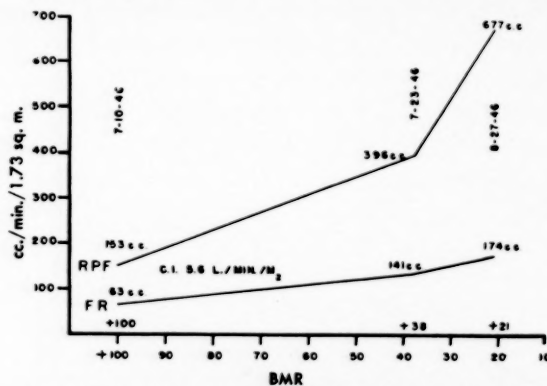


FIG. 2. Despite the high cardiac index the renal plasma flow and filtration rate are decreased to one-fourth and one-half normal levels, respectively. As the BMR fell and the renal plasma flow rose above 200 cc./min., the filtration rate rapidly became normal. The renal plasma flow approached normal more gradually.

as they become compensated, suggesting that a slight decrease occurs as they go into failure.³⁸ Most of them become compensated at absolute bed rest. These have a normal or high renal plasma flow and filtration rate.³⁹ Occasional patients continue to have failure at rest. We have studied one of these and the results are shown in Figure 2. Both renal plasma flow and filtration rate were reduced just as in other cases of chronic congestive failure despite the high cardiac index (cardiac index = cardiac output per square meter body surface). As the BMR fell with administration of Lugol's solution and propylthiouracil, the filtration rate rose sharply and the renal plasma flow increased at a somewhat slower rate. Obtaining multiple data on the cardiac output was impossible because of limited veins of sufficient size, but it is fair to assume that the cardiac output fell as the BMR fell just as it did in Brannon's patients.

Thus we find that as the metabolic demands of the tissues decrease the renal plasma flow and filtration rate rise in severe thyrocardiac patients. Since the metabolic demands of the tissues become greater in

exercise, the renal plasma flow decreases. This decrease is greater in cardiacs than in normal subjects and the former also have a fall in filtration rate. Since cardiac subjects have only limited ability to increase the cardiac output with exercise, it appears from these data that when the patient cannot increase his cardiac output sufficiently for tissue metabolic needs the kidney shuts down. The kidney functions fairly adequately until its blood supply decreases to about 20 per cent of normal.^{40,41} The shunting of blood to more delicate tissues such as the brain may be a very useful thing in times of stress such as shock and heart failure.

The mechanism of renal shutdown in response to an "inadequate" cardiac output is of great interest because knowledge of it may throw light on some of the fundamental processes in heart failure. Several possibilities exist. It could be under sympathetic control, it could be mediated through one of the renal hormones or it might be set off by some other hormone or metabolite.

It is known⁴² that cardiac output may drop as much as 20 per cent if an individual stands motionless at an angle of 60 degrees with the horizontal. The renal plasma flow and filtration rate diminish proportionately.⁴³ This phenomenon resembles what happens in heart failure except that Smith has found the filtration fraction to be normal as a result, he suggests, of afferent arteriolar constriction. However, the filtration fraction (per cent of renal plasma flow which is filtered, normally 20 per cent) may be low because of the fall in blood pressure which occurs.

To test the role of the sympathetic nervous system in these phenomena we⁴⁴ tilted a patient with hypertension who had had a Smithwick sympathectomy. Absence of sweating indicated that the sympathetic nervous system had not regenerated. Despite the loss of sympathetic innervation the same changes in renal hemodynamics occurred as in the normal individual. This was true, too, of a patient with orthostatic hypotension who also failed to sweat below

the fourth dorsal segment. Neither patient had a significant fall in blood pressure so the renal changes cannot be attributed to that.

Further evidence that the sympathetic nervous system is not involved was obtained by producing spinal anesthesia above the fifth dorsal segment in three subjects with congestive failure and diminished renal plasma flow. No increase in renal plasma flow was effected.^{44,45} Since the possibility existed that the kidney blood flow could not increase after so prolonged a shutdown, we gave them 0.72 Gm. aminophylline intravenously to increase the cardiac output.^{46,47,48} The cardiac output rose from 100 to 300 per cent and the renal plasma flow increased as much as 40 per cent without very much rise in blood pressure. In addition to this the fact that the renal plasma flow returned to normal in the thyrotoxic patient described above points to its ability to do so in other types of failure. Thus, the sympathetic nervous system is fairly effectively eliminated.

As mentioned above, renin is found in the renal venous blood of cardiac subjects and not in that of normal individuals. One cannot exclude renin as the cause of these phenomena but the evidence for it is not conclusive.

The posterior pituitary secretion could cause the reduction in renal plasma flow. The great difficulty in assessing its role is that the substances secreted by the pars intermedia of the pituitary are not known. Pitressin, pitocin and pituitrin all may well be artificial substances created by the chemicals used in their isolation. Therefore direct experimentation with these materials might have little significance.

Five patients who stood motionless at a 60 degree angle with the horizontal had striking decreases in the renal plasma flow and filtration rate, with a marked fall in sodium or chloride excretion. (Table I.) The latter persisted for the period following the return to a horizontal position in one patient in which it was measured and in all of Brun's patients.⁴⁹ The plasma flow did not

return to normal for fifteen or more minutes. Blood from Brun's patients produced marked decrease in urine volume in the recipients. The urine chloride excretion per minute was decreased in one patient and remained the same in another. The renal plasma flow and

what the sodium excretion and renal plasma flow did in the patients with diabetes insipidus because it would assist in determining the cause of the various phenomena which occur in the kidney with motionless standing and might help to define the role

TABLE I
THE MECHANISMS OF SALT AND WATER RETENTION IN HEART FAILURE

Patient	Diagnosis	Position	Time (min.)	Renal Plasma Flow	Filtration Rate	Filtration Fraction	Urine Volume	Sodium Excretion	Concentration Sodium Reabsorbate
				ml. per 1.73 sq.m. per min.		per cent	ml. per min.	m.Eq. per 1.73 sq.m. per min.	m.Eq. per L.
W. M. R.	Normal	Flat	10.0	564	140	24.9	13.2		
			10.1	579	144	24.9	14.1	.164	165.5
			9.9	548	131	23.9	14.4	.168	168.8
		Tilted	15.0	437	119	27.3	10.1	.117	163.5
		Flat	15.0	379	113	29.7	5.26	.028	147.0
K. D.	Diabetes (controlled)	Flat	10.2	481	121	25.2	10.2		
			10.1	467	109	23.4	10.6	.128	158.0
			9.7	455	109	24.0	10.9	.131	158.5
		Tilted	15.0	373	112	29.9	10.0	.099	157.0
			15.0	226	72	31.8	4.4	.024	151.7
C. P.	Asymptomatic neurosyphilis	Flat	15.0	868	147	16.9	5.9		
			15.0	746	148	19.8	10.6	.222	157.1
			15.0	763	133	17.5	12.1	.193	161.1
		Tilted	14.8	558	121	21.7	8.6	.108	155.0
			15.2	255	63	24.6	1.6	.016	148.6
		Flat	15.4	386	89	23.0	0.39	.027	145.7
J. M. W.	Gonococcal arthritis (convalescent)	Flat	15.0	706	138	19.5	10.0		
			15.0	718	124	17.3	11.2		
			15.0	664	129	18.6	10.7	.107	159.5
		Tilted	15.0	522	134	25.7	9.7	.082	156.6
			15.0	398	121	30.7	5.46	.022	146.7
			15.0	504	120	23.7	4.07	.015	146.0
D. L. D.	Asymptomatic neurosyphilis with serologic relapse	Flat	14.0	641	138	21.5	6.2		
			15.0	556	127	22.8	9.0	.165	158.3
			15.0	496	135	27.1	9.55		
		Tilted	15.0	526	127	24.1	9.8	.144	159.8
			15.5	463	114	24.6	5.75		
			14.5	417	107	25.2	2.1	.061	149.5

filtration rate were not measured in the recipient. These authors believed that some of the changes were produced by the posterior pituitary because less pronounced changes occurred in patients with diabetes insipidus. It would be interesting to know

of the posterior pituitary in heart failure. With the data at hand it is not possible to make any definite statement.

The possibility that increased adrenal cortical secretion might cause the fall in renal plasma flow in heart failure has been

suggested. This seems unlikely since Hellman et al.⁵⁰ showed that the adrenocorticotrophic hormone will increase the renal plasma flow when the latter is diminished in Simmonds' disease. We⁵¹ have given adrenocorticotrophic hormone to two normal subjects without any appreciable change in renal plasma flow or filtration rate. Also, White, Heinbecker and Rolf⁵² have demonstrated that adrenal cortical extract plus desoxycorticosterone acetate will partially alleviate the reduction in renal plasma flow and filtration rate in adrenal deficient dogs. However, they did not increase the diodrast T_m which was also low. The diodrast T_m is not reduced in constrictive pericarditis with heart failure.⁵³ Furthermore, in Addison's disease the filtration rate is reduced to a greater degree than the renal plasma flow, whereas the reverse is true in heart failure whether the venous pressure is high or normal. Evidence will be given below for a marked increase in adrenal cortical secretion. This eliminates the possibility that a deficiency of that hormone plays a part in heart failure. Neither can the increase be responsible for the renal plasma flow changes for the reasons already given.

White, Heinbecker and Rolf have eliminated increased or decreased thyroid and ovarian secretion as the cause of the type of renal change seen in heart failure. They were not able to rule out a decrease in a special "renotropic" hormone in the anterior pituitary. Deficiency of such a substance offers an attractive hypothesis, as it might be more or less automatically reduced in concentration by a fall in cerebral blood flow. No positive evidence of such a substance has appeared thus far although certain negative evidence points to its existence.⁵²

For the sodium retention in heart failure several possible causes exist. The sympathetic nervous system seems effectively ruled out. The filtration rate as a mechanical factor may be important. The clinical relationship between salt retention and the level of filtration rate has already been shown, although it is true that both could

be due to some other related or common cause. In acute glomerulonephritis salt and water retention may occur, presumably due to a low filtration rate. If adrenal cortical hyperactivity could be ruled out, this offers a particularly good situation for demonstrating the importance of filtration in sodium excretion. Conn has shown that the sweat sodium is a good index of the activity of the sodium-retaining hormone of the adrenal cortex. The sweat sodium is low in Cushing's disease (hyperactivity of the adrenal cortex) and high in Addison's disease (low activity of the adrenal cortex). No overlapping was demonstrated. We have found the sweat sodium to be normal in four of five cases of acute glomerulonephritis with edema⁵⁵ and low in the fifth patient. Thus, the normal sweat sodium concentration constitutes good evidence that the adrenal cortex plays no consistent role in the sodium retention of acute glomerulonephritis and suggests that reduced filtration rate may result in salt and water retention. Further evidence is needed before this can be considered settled. A patient with rheumatic heart disease and chronic heart failure was followed for three years with four different series of renal studies and consistently had a moderate reduction in renal plasma flow to 348 and a striking reduction in filtration rate to 49 cc. per minute. The low filtration fraction is the reverse of what is expected in heart failure and it was thought that she had a healed glomerulonephritis with the low filtration rate which may accompany it.^{56,57} Ordinarily sodium retention does not occur in heart failure at rest with a renal plasma flow above 200 to 225 cc. per minute. The fact that in spite of the above this patient had to have mercurial diuretics twice a week, although she did no work, points to a filtration factor operating in her sodium retention. One other patient with a renal plasma flow of 253 cc. per minute and a filtration rate of 65 cc. per minute with a normal sweat sodium also had chronic sodium retention. This patient had been studied twice, with the same results. These

findings again indicate a filtration element in the sodium retention of heart failure. The fact that a very low renal blood flow and filtration rate may occur in renal disease without edema is not opposed to this idea. In renal disease the tubules may also be damaged and unable to handle sodium normally,^{58,59} whereas in heart failure most tubular functions other than diodrast T_m are normal.^{2,40}

We now have four patients, three with low filtration rates and chronic heart failure who have very low sweat sodium concentrations.⁶⁰ Five subjects with less severe failure with relatively normal filtration rates have normal or high sweat sodium concentrations, indicating that the adrenal cortex comes into play in heart failure very late. We were unable to demonstrate any appreciable change in the sweat sodium concentration with exercise. Thus hypoactivity of the adrenal cortex cannot account for relatively normal resting renal blood flow and filtration rate in patients with heart failure, although it may be that there is a lag between stimulation of the adrenal cortex and the change in sweat sodium concentration. It is likely also that adrenal cortical stimulation occurs in coryza and other infections and injuries which are known to increase failure in the cardiac patient. In fact the sweat sodium of one severe cardiac patient with a low sweat sodium fell to one-half its previous level when the patient developed a skin infection of the cubital fossa.⁵¹

One more possibly major factor will be considered in the edema of heart failure—the antidiuretic hormone of the pituitary. It is not believed that this alone can produce sodium retention, and water retention *per se* does not usually produce edema. However, if a severe cardiac subject is rendered partially free of edema with mercurial diuretics, he may then become apparently unresponsive to mercurial diuretics. If mercurial diuretics are continued, the blood sodium will gradually fall. In one of our patients it reached a value of 118 mEq./L. and in another 114 mEq./L.

(our normal = 137 to 143 mEq.). Despite this, in both no water diuresis occurred although sodium excretion was increased about tenfold and she was still edematous. Several possibilities exist to explain this: the antidiuretic hormone of the posterior pituitary could be responsible; the normal balance between the proximal and distal convoluted tubules could be disturbed by the mercury which apparently acts on the proximal convoluted tubules only; or it is possible that a disturbance in intracellular electrolyte metabolism may be involved. It is not definitely known that such a disturbance can produce edema. That intracellular electrolyte imbalances may enhance heart failure has been demonstrated in animals. Desoxycorticosterone may cause sodium retention with potassium loss producing areas of myocardial necrosis and heart failure.^{61,62} The same thing is thought to occur in other types of sodium retention and potassium deficiency and could occur in a cardiac subject with sodium retention and superimposed potassium deficiency due to nausea and low intake. In such states the patient may become irrational. In cardiac delirium relief of massive edema with diuretics usually produces improvement. This is probably not due to improvement in cerebral circulation since the cardiac output does not change appreciably under these circumstances. The change could be caused by correction of an intracellular electrolyte imbalance.

The question is frequently asked, Is salt and water retention useful in heart failure or is it an error of metabolism? Landis⁶³ thinks that it is beneficial in the standing cardiac subject but that it may be dangerous when the patient lies down. Starling,⁶⁴ Borst⁶⁵ and McMichael⁶⁶ all believe it to be a good thing and essential to maintenance of the cardiac output or the most favorable blood volume possible under the circumstances. They all accept the thesis that cardiac output is very sensitive to the level of atrial filling pressure, increasing as the latter increases until severe failure sets in at which time the cardiac output falls. Within

wide limits Warren, Stead, Weens and Brannon^{67,68} have been unable to demonstrate this relationship. Marked increases in atrial pressure as a result of rapid saline infusions and marked decreases from rapid withdrawal of venous blood did not change the cardiac output. For this reason we are inclined to take the view that salt and water retention is an error of metabolism. We believe that the renal blood flow shutdown mechanism and salt and water retaining mechanisms may be useful in combatting the low cardiac output of shock or perhaps simply in assisting in the adjustments to the low cardiac output of standing. In these cases a low cardiac output does result from a low circulating blood volume and salt and water retention would be useful. In cardiac failure low cardiac output results from intrinsic heart disease and we should not expect the rise in venous pressure to change this condition. As a matter of fact, elimination of excess salt and water and high venous pressure with mercurial diuretics produces no appreciable change in cardiac output and renal hemodynamics of the patient. Furthermore, clinically the patient seems greatly improved and no inconvenience is noted in either the horizontal or vertical position. The nearer the blood volume and venous pressure are brought to normal, the better the patient feels although his cardiac output remains essentially the same. One would expect him to feel worse if the rise in blood volume and venous pressure were useful.

SUMMARY

The concept is proposed that edema in heart failure is caused by retention of salt and water produced by a diminished ability of the kidney to excrete salt and water. This disturbance in the kidney is the result of an inadequate cardiac output which is both *relatively* and *absolutely* reduced in patients who have chronic cardiac edema at rest, and is *relatively* reduced as compared with general or specialized tissue demands in other cardiac subjects with edema, i.e., those who fail with exertion, hyperthyroid-

ism, anemia or beri-beri, and who may have a normal or elevated resting cardiac output. The inadequate cardiac output, through one or more mechanisms, causes the kidney to excrete less salt and water. It also produces a reduction in renal plasma flow and filtration rate by a contraction of the efferent arterioles of the kidney effected by some humoral substance. The reduced filtration rate corresponds closely to the reduction in sodium excretion and evidence is presented which indicates that the lowered filtration rate may be one of the causes of the reduction in sodium excretion. In advanced stages of heart failure the reduction in salt and water excretion is probably produced by at least two other means—the adrenal cortex is definitely stimulated and the pars intermedia of the pituitary probably also plays a part. Much work needs to be done to evaluate the role of these various factors both in renal hemodynamics and sodium excretion. Too little is known of the effect of changes in the intracellular electrolytes on edema formation and cardiac physiology to warrant any speculation as to the part taken by them.

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Clinic on Psychosomatic Problems

A Case of Duodenal Ulcer with Anxiety Attacks Treated by Psychotherapy

THE clinics are designed to bring out psychosomatic relationships both in symptomatology of the patient and in the organization of the hospital. Reports are directed by Drs. Stanley Cobb and Allan M. Butler and are edited by Dr. Henry H. W. Miles. This is a report of a staff meeting of the Psychiatric Service of the Massachusetts General Hospital. The preparation of these psychosomatic case histories receives support from the Josiah Macy, Jr., Foundation.

DR. AVERY D. WEISMAN: L. F., No. 518808, a thirty-year old farm worker was admitted to the hospital complaining of attacks of palpitation for the past three months and of epigastric pain previously diagnosed as duodenal ulcer since the age of fifteen.

The first anxiety symptoms occurred while the patient was convalescing in a hospital from a minor back injury which, according to his wife and the family doctor, had been unduly disabling. There was a sudden onset of faintness, palpitation, an "alarming sensation" in his chest and dread of death. The attack lasted two days after which he remained in the hospital three weeks because of a severe headache following lumbar puncture. After discharge he felt too weak to return to work.

During the next two months there were three more severe anxiety attacks, each with the same apprehensiveness and fear of death. An intense desire to defecate preceded and accompanied each spell. With the last episode the patient suddenly fainted. His wife described him as pale and sweaty, with no tonic or clonic movements.

The patient had first noted epigastric pain and a sensation of constriction about the lower chest when he was fifteen years old. The symptoms were relieved by belching and by eating and were definitely related to emotional upsets. A positive diagnosis of duodenal ulcer was made five years later, and for a year he followed a bland diet with relief of symptoms. He then began using alcohol regularly and the ulcer

symptoms recurred. They continued intermittently from that time on, with a number of severe exacerbations including a hemorrhage, in temporal relationship to troubles with his first wife. The patient was hospitalized many times because of his ulcer. One year before the present admission a laparotomy had been performed for suspected perforation but none was found. At that time he had had financial difficulties and his wife had been sick. The patient was aware of the relationship between situations and his ulcer symptoms, saying: "When things go bad, my ulcer goes bad." He had noticed that during the anxiety attacks his abdominal pain disappeared, and this only frightened him more since he interpreted the absence of pain as a sign of imminent death.

Past medical history included the usual childhood diseases and otitis media at the age of fourteen. He had had a large number of accidental injuries and various fractures. Eight years before the present admission he was said to have had pulmonary tuberculosis and was treated by pneumothorax. Subsequent x-rays had all failed to show evidence of an active lesion.

Social history disclosed many factors associated with the patient's symptoms and behavior patterns. He was the youngest of three children born to an alcoholic ne'er-do-well father and a promiscuous mother who separated when the patient was eighteen months old. The elder siblings were sent to foster homes but the patient was placed in a large state institution where

homeless children had to mingle with cretins, epileptics and idiots. He was unhappy and fearful there. He was afraid of the dark and afraid of strangers. He walked in his sleep, had nightmares and enuresis. There were also gastrointestinal symptoms such as anorexia, food-fussiness and vomiting.

In the institution discipline was severe and beatings were customary. When the patient first developed abdominal pain, he did not ask for medical attention for fear of added punishment. He remembered that some of the feeble-minded boys ate in an offensive manner, gulping their food like animals and sometimes drooling into their bowls. At times he became so disgusted, angry and rebellious that his pain increased markedly and he vomited. If seen by an attendant, he was forced to eat his vomitus.

Finally when he was nineteen he got into a fight with an attendant and was trying to kill him when other guards intervened. He then ran away but was soon apprehended. A sympathetic judge paroled him to a farm for two years where he was fairly happy.

At the age of twenty-one he set out to find his parents only to discover that he could not get along with either of them. Then followed a period of wandering about the country doing unskilled labor. For a few weeks he worked for a farmer, becoming very fond of the latter's wife, whom he called "mom." He felt as if he had found a home and was bitterly disappointed when the farmer discharged him. He vowed that someday he would return and take his "mother" to live with him as she had confided that she was unhappy with her husband. Several years later when he returned to New England she left her husband and came to stay with the patient and his wife.

The patient was married when he was twenty-five and was sorry almost immediately. He suspected that his wife was unfaithful but never voiced his suspicions. Eighteen months later he left her without trying to get a divorce. During the brief marriage he was in and out of hospitals

chiefly because of ulcer symptoms and also for injuries sustained at work. After leaving his wife he was depressed and lonely and became a hobo, working only enough to buy liquor which he drank to excess. Stirred by the attack at Pearl Harbor he enlisted in the Marine Corps but was discharged two months later because of the duodenal ulcer. During this brief service he was in trouble for impulsively striking a non-commissioned officer.

He then formed a bigamous relationship with a farm girl who became his common-law wife. They hitch-hiked around the country for a year with no ties and no responsibilities ("the happiest period of my life") and finally settled in New England. They had two children, and after the birth of the second the patient's adopted mother came to live with them. The patient's wife worked and became fairly successful financially while he remained an unskilled laborer.

Physical examination revealed a muscular, well proportioned man who was tense but not acutely ill. The only findings of significance were a right pararectus scar, slight epigastric tenderness and loud peristaltic sounds.

Urinalysis and complete blood count were normal. The Hinton test was negative, and three stools were negative for occult blood. Electrocardiogram and electroencephalogram were considered normal. The basal metabolic rate was -17 . Chest x-ray revealed an area of increased density in the right apex, apparently an old, healed tuberculous infection. X-ray examination of the gastrointestinal tract showed prominent gastric rugae but no evidence of a gastric lesion. The duodenal cap was constantly deformed and a persistent fleck of barium indicated an active ulcer crater.

The patient remained five weeks in the psychiatric ward during which time there were twenty-eight therapeutic interviews of an hour each. In describing the setting of the first anxiety attack the patient brought out feelings of helplessness associated with fear that his back had been injured perma-

nently. He had been worried over his financial straits and had fantasies of wife and children being left destitute should he die. There were also fears that his first wife would locate him and prefer charges of bigamy. A strong feeling of dependence upon his second wife was expressed. The associations then led back to experiences in the institution where the boys were frequently whipped on the buttocks. They were made to line up and bend over, and while waiting his turn the patient sometimes defecated involuntarily. He also recalled that one of the matrons used to punish by inserting a short stick, smeared with laundry soap, into boys' rectums. This produced cramps and defecation. (It is interesting how this material correlated with the desire to defecate associated with the anxiety attacks, and with the patient's impulsive outbursts when startled by an approach from the rear.)

It was pointed out that his feelings of being helpless and afraid in the face of current life situations were associated with the anxiety attack, and that the latter, essentially, was the physical expression of fear, helplessness or apprehensiveness. Further discussion of the anxiety symptoms utilized current material. After an anxiety attack one night in the ward he told of feelings of disappointment that his wife had failed to visit him and his uneasiness because he could not reach her by telephone. His associations went on to fantasies of being attacked by a fearful animal and of being dead. (Being left alone, i.e., "helpless," stirred up his anxiety.)

The ulcer symptoms were then investigated and the patient recalled that his first abdominal pain was associated with fantasies of smashing the skull of a hated gym instructor at the institution. He talked about various men in his life who have tried to put things over on him. "When they seem to be decent, then they fail me." Later he expressed doubts about his treatment and had fantasies that the therapist did not wish to help him. This distrust was discussed in the light of past feelings. His own words

were used to illustrate: "Men I trust put me behind the eight-ball." The patient accepted the interpretation, admitting that consciously he knew his misgivings were unrealistic.

Various periods in his life when the ulcer symptoms had been either severe or in remission were taken up in detail. They were very bad during his first marriage. He knew his wife was unfaithful and he was very unhappy but was unable to do anything until he actually caught her with another man. Then he simply walked out without seeking legal recourse. He endured the unhappy relationship because of a longing for a companion and a home, "things I'd never had before." He also spoke of his adopted mother. "She was the first woman I could ever talk to." He felt well while staying with her and her husband but then the latter became jealous and got rid of him. The ulcer symptoms returned promptly.

A ward incident then furnished utilizable material. He was forbidden to play poker and was much angered by the nurse's "superior attitude"; his ulcer pain returned temporarily. In discussing the incident his associations led back to memories of the institution where he was helpless in the face of brutal authority. (Impotent rage in reaction to the threat of force seemed to be the important emotion.) Interpretation was made that his feeling of being abused led to rage and feelings of insecurity and that these were associated with the ulcer symptoms.

Another time the patient became angry because there was fish for lunch. It was a food he detested and he developed a painful, "tight feeling" in the lower chest. Again the associations led to his disgust with the food at the institution and his impotent anger. It was pointed out to him how in many ways he still reacted emotionally as he did long ago. He accepted this interpretation but then asked: "Why do I do it? Why can't it all come out—and get it over with?"

A number of interviews were devoted to investigation of his numerous hospitalizations and injuries and it seemed clear that

several were escape reactions at times when the patient could not cope with his problems. He told of his sexual experiences and said that he was once supported for three months by a prostitute. The fact that she preferred him to all the other men made him proud of his sexual ability, and it was noted that during this period his ulcer was asymptomatic. He expressed guilt over his behavior during the first marriage, saying that if he "had been a man" he would have insisted on a divorce. He had had fantasies of killing his wife and her lover but actually could not bring himself to do anything at all except walk out. (It was evident that the patient had strong feelings of dependency and could not wholly accept them. When his dependent needs were satisfied, his ulcer symptoms were better; when there was a conflict, the symptoms became worse.)

At this point in therapy the patient was presented at a staff conference. Symptomatically, he had improved considerably although a repeated gastrointestinal series showed the ulcer crater unchanged in size.

Presentation of the Patient. The patient entered the conference room with an air of composure. A slight tremor in the voice and some tenseness of posture were the only evidences of nervousness. Considering his social and economic background his choice of words and manner of speech were remarkably good. He answered questions without hesitation or embarrassment and seemed anxious to make a good impression.

DISCUSSION

DR. JAMES A. HALSTEAD: Has he not had long remissions when his stomach was better?

DR. WEISMAN: He has had a number of periods of security—when he lived with the woman who was his adopted mother, and with his second wife going around the country without responsibility; also at other times when he met older women who supported him. He worked once for an older doctor and was well then.

DR. HALSTEAD: I performed a gastroscopy on him. The mucosa was absolutely

normal; there was no increased redness. About 50 per cent of the people with an active ulcer will show changes of the mucosa. The x-ray does show an active ulcer even though his symptoms are now inactive.

DR. JACOB E. FINESINGER: Did you make any interpretations to him?

DR. WEISMAN: Only by throwing things back at him, reminding him of something he had said before.

DR. EDWARD HITSCHMANN: Such people are described in the literature. They have no ideal in childhood. Usually they develop into psychopaths or occasionally criminals. They have no mother and cannot identify with an honest father. This question is important here; and I fear that unless we hear more about his character and his morals, we will be unable to understand the mechanisms of his neurosis, because these people are not as clearly developed as the usual neurotic who has a conscience or superego. This case is more interesting because ulcer beginning at fifteen is rare. He may now have changed his character so that he is capable of anxiety, self-reproach and guilt feelings. Such cases have been described as finally cured by a kind mother. There are some allusions to this possibility here. With such parents, I would name him a psychopath.

DR. FINESINGER: How did his older brother turn out?

DR. WEISMAN: He seems more reliable than the patient although he gets mixed up in get-rich-quick schemes.

DR. HITSCHMANN: I do not believe that the anxiety is so important. Ask him about his conscience, whether he has guilt feelings.

DR. WEISMAN: His wife objects to his overabundance of guilt. He will go out with another woman and insists on coming home and telling about it. She objects to his little boy attitude of confessing and getting dispensation.

DR. MARIANNA TAYLOR: I should think of him as a psychopath. When you see and hear him he seems effeminate and passive.

DR. FINESINGER: There is a good deal in

that. He plans to go to California to open a gift shop because his wife and adopted mother want it.

DR. HENRY M. FOX: Do you feel that what you have done will hold water when you send him out? How much depends upon his being in the situation of dependence on you?

DR. WEISMAN: When he had been in the ward a week or so he had to return early from a week-end because of anxiety. He was out last week-end and got along very well. He had an argument with a garage mechanic without any anxiety.

DR. FINESINGER: Dr. Weisman tried to get relationships between symptoms and precipitating events. Today the patient is able to see the events associated with the ulcer and with the anxiety episodes. The question is what should be the next step therapeutically? What do you think about a fifteen-year old boy developing an ulcer?

DR. HALSTEAD: It is unusual at fifteen to have an ulcer but not enough to rule it out. I also think he will have recurrences for a long time.

DR. FINESINGER: In our few ulcer patients who have had typical neurosis the ulcer symptoms seemed to increase with anxiety symptoms, but here is one fellow whose ulcer seems to get better when he is anxious.

DR. WEISMAN: It depends upon the kind of anxiety. It is hard for the average individual to know when he is feeling anxiety. Is it not true that anxiety swallows up all sorts of affect and thus may mask a more specific type of emotion?

DR. FINESINGER: The term anxiety is loosely used to describe a variety of conscious feelings. It is also used, especially in psychoanalysis, to designate an unconscious feeling which is inferred to exist from specific actions of the patient. Tension states, feelings of general discomfort, feelings of avoidance, hesitation and frustration are among those considered as anxiety. It may be that intensification of feelings of this kind is associated with exacerbations in ulcer symptoms. We have limited, in this case presentation, the use of the term anxiety to

the alarming sensations, feelings of dread and of fright that usually occur in attacks characterized primarily by cardiovascular symptoms. In anxiety attacks the sensations may be so disturbing and the patient's attention focussed on them to such a degree that more subtle types of emotion are not experienced and reported. I believe that is the sequence of events occurring in this patient.

DR. BERNARD BANDLER: My feeling about the anxiety is that it may be prodromal to a psychosis, possibly to alcoholic psychosis. If he did have one, he might have hallucinosis with emphasis on paranoid features. In terms of therapy, as long as Dr. Weisman continues with him, he should do fairly well. The danger is that he may be separated from the doctor. As long as he has confidence in his doctor he will continue to be better.

DR. HERBERT BARRY: This man has at least two and probably three disparate conditions. He has a typical psychopathic personality, almost a textbook picture. As such his statements must all be suspected. Psychopaths are notorious liars. The prognosis is bad. He will go to California and lose track of therapy and get into difficulties. He also has an ulcer. The third thing he has is anxiety neurosis which might be incipient psychosis. The attacks of anxiety are the chief reason he has been willing to stay on the ward. I would not be too hopeful about the outcome.

DR. FINESINGER: His is a complicated case. The striking thing is that this man up to a few months ago did not have frank anxiety symptoms. As to personality, I believe as we all do that he tends to the psychopathic side of the scale. Psychopathic personalities are usually characterized by the absence of feelings of guilt, even in the amount necessary for normal social conformity. The lack of guilt is explained by the failure of the patient to identify in childhood with parents or other figures who furnish ideals for social behavior. This may be due to a disturbance in the capacity for identification or to the absence of suitable

figures in the childhood environment. In contrast, patients with psychoneurosis or psychotic depressions have an undue amount of guilt feelings to which they react with a need for punishment. Often the symptoms fulfill this need. Anxiety symptoms may represent the fear of punishment. These patients have identified in childhood with parents who were too demanding or too strict. Thus too much guilt leads to neurosis or depressions; too little guilt leads to the development of psychopathic personality. In the treatment of psychopathic personalities one of the goals is to "mobilize" the patient's guilt feelings. When this occurs, anxiety symptoms may appear. The fact that this patient has frank symptoms of psychoneurosis makes me believe that the outlook is not so hopeless. To date he illustrates the limitations of certain therapies. Can we go beyond pointing out a correlation between symptoms and situations? The thing to decide on is the next therapeutic move. Can we not do more? More insight? I am not sure if it is possible but it is worth trying. If he would stay, I would keep him until I had gone into the dependency problem. I would attempt insight therapy dealing with his dependency and his reactions to it.

DISPOSITION AND FOLLOW-UP

The patient stayed in the ward about a week longer and the interviews were directed toward the problem of his dependency. The exacerbation of symptoms which had resulted in the laparotomy was reviewed and it was suggested to the patient that the important factor at that time was that the whole load of caring for the family fell upon him. The following interpretations were made: Anxiety symptoms or illness (the ulcer) seemed to appear when he had to make independent decisions or assume responsibilities. (Examples of this reaction were cited from the interview material, as nearly as possible phrased in his own words.) It was pointed out how he had wanted someone to take care of him and had wanted no responsibilities. Actually this state could

be obtained in childhood, and a normal childhood was something he had missed and had always longed for. When his responsibilities weighed upon him, anxiety resulted—the fear that he could not adequately cope with his obligations. One solution to the problem had been sickness (examples were given from the material showing how his ulcer symptoms and some injuries served this purpose.) It was pointed out, also, how his numerous fantasies and worries about disease suggested that if he could develop disease his problem might be solved, i.e., he could then be dependent in a legitimate manner.

The patient did not agree with the interpretations but nevertheless left the hospital much improved. His anxiety was mild and the ulcer symptoms had disappeared. He went back to work and when seen a month later was still feeling well. He has not returned. A year and a half after discharge he reported that he was working regularly and did not feel the need for further treatment.

SUMMARY

A patient with a duodenal ulcer and anxiety attacks was treated by a conventional medical regimen (diet and antacids) and by brief psychotherapy. This case was selected to illustrate important points in the psychiatrist's technic. Essentially what he did was to encourage the patient to talk freely, always with the emphasis upon emotionally charged topics, until the detailed material thus obtained provided a clear correlation between symptoms and repetitively recurring behavior patterns. This correlation was then pointed out to the patient, i.e., "interpreted." It is important to note that the interpretations were not based upon preconceived theories of the psychiatrist but were in fact made only from the material produced by the patient in the interviews.

It is believed that when the relationship between emotion-provoking events and the reactions of the patient are understood, a modification of the symptoms and improve-

ment of personal and reality adjustment may result.

In this case the patient had good insight into the temporal relationship of symptoms and situations. His formula was: "When things go bad my ulcer goes bad." This was true but he had been unaware of the basic conflict which was uncovered in the interviews. On one hand he had an extreme desire for dependency and security and on the other a wish for freedom and no responsibilities. In certain situations in which he could accept his dependent needs he got along without symptoms. Sometimes the conflict was "solved" by illness, either

ulcer or anxiety attacks. The formula might then be expressed: "If I am sick, then I can be dependent legitimately."

A good doctor-patient relationship developed in which the patient who had never had satisfactory relationships with men came to trust and depend upon the therapist. It is possible that a good deal of the success in this case depended upon this relationship. When such a patient finishes treatment and loses the sustaining therapist, one must keep in mind the possibility of a flare-up of symptoms. It may be necessary to continue seeing the patient at infrequent intervals for "supportive" interviews.

Clinico-pathologic Conference

Pneumonia and Empyema*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, A. M., (B. H. No. 162439), was an eighty year old, unemployed, white male who entered Barnes Hospital on August 15, 1948, complaining of cough, chest pain, chills and fever. The family history revealed that the patient's mother had died at the age of sixty-eight from a "stroke." His father had had known tuberculosis for many years but died at fifty-two from carcinoma of the stomach. One brother had died at the age of sixty-two from cancer of the kidney. During his long lifetime the patient had enjoyed relatively good health until his latter years. He stated that he had had "head colds" every winter and for twenty years he had noted pain in the front of his chest which was unrelated to exertion and was never severe. During a similar period he had had dyspnea on moderate exertion, but at no time had he experienced orthopnea or paroxysmal nocturnal dyspnea. He had had some frequency and dysuria intermittently for a number of years. All of the symptoms listed had progressed only slightly. The patient had worked in a shoe factory until the age of seventy at which time he retired.

Four years before admission to the hospital the patient had an upper respiratory infection following which he developed a cough which persisted. The cough was productive of approximately one-fourth of a cup of grey mucoid sputum daily, but the sputum was never bloody; the cough was most severe in the morning, particularly during the winter. Over the course of the four-year period dyspnea on exertion gradu-

ally increased until it became marked, and for three years the patient had rather persistent ankle edema. Five months before his admission to the hospital he came to the Washington University Clinics because of cough and dyspnea. Examination revealed signs which suggested cardiac decompensation. A film of the chest showed a prominent shadow at the right hilar region. There were also increased markings at the right base which were thought to be compatible with pneumonitis. The patient was referred to the chest clinic. The hilar shadow was thought to be vascular in origin and a diagnosis of emphysema was made. Because of his urinary complaints, he was also referred to the genito-urinary clinic; no significant abnormalities were found. The patient was given medication for relief of his cough and he improved somewhat. While attending the clinic, however, he lost 20 pounds and became noticeably weaker.

Four days before entry the patient fell into the river while fishing and swallowed a considerable amount of cold, muddy water. The two friends who had accompanied him on the fishing trip were elderly and were unable to pull him out of the water; he was thus forced to remain partially immersed for about one hour. The return trip to his home consumed several more hours and by the time the patient arrived he had begun to have chills and to feel feverish. Soon thereafter he noted pain in the left lower chest which was pleuritic in character. His cough increased in severity and sputum became profuse

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and discolored. His symptoms grew worse and the pain spread to involve the entire thorax; it was particularly severe on the left side. One day before admission he coughed up a cupful of thick, brownish sputum. Because of his weakness and chest pain the patient found expectoration very difficult. He was seen by a physician who gave him an unknown amount of penicillin and apparently performed a thoracentesis but no information in regard to the procedure could be obtained.

On admission to the Barnes Hospital the patient's temperature was 37.5°C., pulse 92, respirations 22 and blood pressure 90/50. The patient was a well developed but poorly nourished elderly male in moderate respiratory distress lying flat in bed. He complained of pain in the left chest. The skin was pale. There was edema of the legs, sacrum and scrotum as well as of the lower left chest wall posteriorly. Edema was also noted in the left axillary region which was tender on palpation. The pupils reacted well to light and to accommodation. Examination of the fundi revealed narrowing and tortuosity of the arterioles. The nose and throat appeared essentially normal. The mouth was edentulous. The neck veins were not distended. The trachea was in the midline. Respiratory excursion was unequal, being greater on the right than on the left and there was hyper-resonance to percussion over the right lung. The left side of the chest was dull to percussion from below the level of the fifth rib posteriorly and the second rib anteriorly. Over this area there was a loss of tactile fremitus, voice sounds were diminished and breath sounds were distant and tubular. Rales were heard at the right base. The cardiac borders could not be determined by percussion and the heart sounds were distant. No murmurs were audible. The rhythm was regular. Examination of the abdomen revealed it to be held rather tensely but no organs or masses were felt. The inguinal rings were both large. The prostate was approximately twice normal size but rectal examination was not otherwise remarkable. Aside from absent

knee and ankle jerks the neurologic examination was within normal limits.

Laboratory data were as follows: Blood count: red cells, 3,300,000; hemoglobin, 7 Gm.; white cells, 11,200; differential count: juvenile forms, 10 per cent; stab forms, 36 per cent; segmented forms, 54 per cent. Urinalysis: albumin, negative; sugar, negative; centrifuged sediment, many white cells with numerous clumps. Urine culture: no growth. Stool: guaiac faintly positive. Blood Kahn test: negative. Blood culture: negative. Sputum smear: many cocci in pairs and clusters; sputum culture: *Bacillus proteus* and coliform organisms. Blood chemistry: non-protein nitrogen, 36 mg. per cent; total proteins, 4.8 Gm. per cent; albumin, 2.3 Gm. per cent; globulin, 2.5 Gm. per cent; chlorides, 101 mEq./L.; carbon dioxide combining power, 26.6 mEq./L.; calcium, 8 mg. per cent; phosphorus, 4.7 mg. per cent; alkaline phosphatase, 3 Bodansky units; acid phosphatase, 2 King-Armstrong units; cephalin-cholesterol flocculation test, 2+; thymol turbidity, 2 units; icterus index, 4.5 units. Prothrombin time: 44 per cent of normal. Coagulation time: three and one-half minutes. Bleeding time: one and one-half minutes. Blood indices: mean corpuscular volume, 115 cu. micra; mean corpuscular hemoglobin, 35 gamma gamma; mean corpuscular hemoglobin concentration, 30 per cent. Electrocardiogram: abnormal form of ventricular complex as evidenced by a low upright T wave in lead I and inverted principle components in leads II and III.

Respiratory isolation was instituted and the patient was given large doses of penicillin parenterally. Fluids were forced by mouth. Thoracentesis was performed and 100 cc. of cloudy yellow fluid were removed. Examination of the fluid revealed large numbers of polymorphonuclear leukocytes. On culture *B. proteus* was recovered. No tumor cells were identified on microscopic examination of a cell block section. On the day following entry the patient's red cell count was 2,470,000 with 8 Gm. of hemoglobin. The white cell count was 5,750 with

a marked left shift in the differential count. Another sputum culture was reported as showing beta-hemolytic streptococci and coliform organisms. On the third hospital day a second thoracentesis was performed. Three hundred cc. of cloudy, greenish purulent fluid with a foul odor were obtained and 200 cc. of gas were also removed. The white cell count on the pleural fluid was 5,800 and culture revealed coliform organisms. Eighty thousand units of penicillin and 0.1 Gm. streptomycin were instilled into the pleural space. Following the procedure, the patient developed extreme weakness, cyanosis, gasping respirations and his pulse became thready. His blood pressure fell to 60/30. Large amounts of mucus were aspirated from the pharynx and trachea and oxygen was given by nasal catheter. The patient also received parenteral streptomycin, blood transfusions, caffeine, adrenal cortical extract and desoxycorticosterone acetate. His condition remained essentially unchanged; tracheal suction was repeated as indicated.

Dependent edema increased although the venous pressure was only 110 mm. of water and the neck veins were not distended. During the fourth day the patient was noted to have developed stiffness of the neck and a lumbar puncture was performed. The initial pressure was 300 mm. of water and the final pressure 250 mm. of water. The spinal fluid was entirely negative. During his hospital stay the patient's blood pressure had never risen above 90/50. His temperature rose to a peak of 39.2°C. on the third day and fell gradually until death which occurred later on the fourth hospital day, August 19, 1948.

CLINICAL DISCUSSION

DR. W. BARRY WOOD, JR.: Before we begin our discussion of this case I should like to ask Dr. Grunow to comment on the x-ray films.

DR. OTTO H. GRUNOW: A chest film taken on the day of admission showed that the cardiac silhouette was obscured by fluid which occupied the entire lower half

of the left chest. A lateral view of the chest showed a distinct fluid level superiorly and some areas of decreased density which were suggestive of encapsulated fluid. In the lateral view there was also evidence of pneumonic infiltration in the posterior sulcus.

DR. WOOD: In this case, in contrast to the situation which often obtains, we have a very excellent history. I particularly should like to read part of the present illness as it was described by a senior student who was a clinical clerk on the ward to which this patient was admitted:

"The present illness proper began four days prior to entry when the patient and two friends went fishing in the country. He had had few complaints in the preceding few days and felt quite well. He accidentally stumbled, however, and fell head first into the stream, swallowing quite a lot of the rather muddy cold water. He regained his feet but could not climb back onto the bank. His friends, both elderly, were unable to pull him out and ran for help. Finally after about one hour, he was pulled from the water. Within a few minutes he began to have chilly sensations but no shaking chills. His cough became marked and was productive of a small amount of thick, brown sputum. It began to rain and the three men waited about an hour until the rain stopped before taking the bus back to the town in which they lived. The patient's cough meanwhile became increasingly severe; he felt feverish and had mild shaking chills.

"When he reached home, he was immediately put to bed and an electric heating pad was used for increased warmth. Within six or eight hours his lower left chest began to pain with each respiration and his muscles and joints ached. The cough continued to increase in severity and the sputum became gradually more profuse and browner (? rusty) in color. The chills increased in severity and frequency and the patient felt hot and sweated moderately. His temperature was not taken.

"He spent an extremely restless night because of the chest pain and cough, and

the following day was very weak and anorectic. He noted the onset of constant hiccoughs. His symptoms grew increasingly severe and respiration and cough became more painful because of chest pain. The pains gradually spread to cover both lower chest regions and radiated to both shoulders. Pain was most marked over the left chest. There was no nausea or vomiting and the patient was apparently not irrational at any time. On the third day his symptoms continued unabated and he brought up about one cup of thick brownish sputum which was not foul. He felt extremely weak and found it difficult to cough because of weakness and chest pain. On the morning of the fourth day, he was brought to the Barnes Hospital by ambulance."

I believe that this very graphic and complete description of the present illness quite clearly points to the primary diagnosis but since some of the problems involved are fairly complicated, it might be well to consider briefly each of the four phases of this man's illness. The first phase began four years prior to his entry into the hospital and was characterized by cough, dyspnea and later edema. During the second phase the patient was seen in the clinic and the abnormal finding on the chest film was described for the first time. The third phase followed the patient's falling into the stream and the final phase became apparent only after thoracentesis had been performed in the hospital. If we can interpret the clinical data correctly during each of these four phases, we should reach the correct diagnosis.

Dr. Scott, this patient had complained of cough for four years and had produced rather copious amounts of sputum which had never been bloody; in addition, he had had dyspnea and for three years ankle edema. How would you explain these findings?

DR. VIRGIL C. SCOTT: In a patient of this age we should first consider emphysema.

DR. WOOD: The radiologists seem to substantiate your impression that the patient had emphysema.

DR. SCOTT: Second, there seems to be

evidence of chronic inflammation of the bronchi which took the form of bronchitis, perhaps associated with bronchiectasis.

DR. WOOD: Dr. Flance, do you agree with Dr. Scott's interpretation?

DR. I. JEROME FLANCE: Yes, I would certainly think that this patient had chronic bronchitis and probably bronchiectasis.

DR. WOOD: If it is assumed that this patient had both bronchitis and bronchiectasis, I should like to ask Dr. Goldman if he is disturbed by the absence of clubbing.

DR. ALFRED GOLDMAN: The absence of clubbing is somewhat disturbing and, likewise, the fact that the patient did not have purulent sputum does not seem entirely consistent with the diagnosis of bronchiectasis.

DR. WOOD: According to the history, the patient's sputum was not purulent. Dr. Rouse, do you have any further information regarding this point?

DR. ERNEST T. ROUSE: At no time were we able to elicit a history of purulent sputum.

DR. GOLDMAN: In regard to the problem of bronchitis and bronchiectasis it should be emphasized that it is often very difficult to be certain whether the transition from bronchitis to bronchiectasis has occurred.

DR. ROBERT A. MOORE: I would agree with Dr. Goldman in that regard. There is no distinct line pathologically between bronchitis and bronchiectasis.

DR. WOOD: Dr. Goldman, what is your view in regard to the hilar mass which was described on the chest film taken when the patient was seen in the clinic?

DR. GOLDMAN: I believe that the shadow represents a pulmonary vessel rather than a tumor. I do not believe that it is suggestive of bronchogenic carcinoma.

DR. WOOD: Do you not think, however, that bronchogenic carcinoma deserves consideration in view of the patient's weight loss and anemia? Dr. Grunow, what is your opinion?

DR. GRUNOW: It is often difficult on roentgen examination to differentiate a mass due to a large vessel from that due to a tumor. I believe, however, as does

Dr. Goldman that in this particular case the shadow represents a vascular marking. Further, the fact that the hilar mass was on the right side and the patient's subsequent pulmonary lesion developed on the left side would seem to me to be against the diagnosis of tumor.

Dr. WOOD: Let us now consider the third phase of this man's illness which began after he fell into the river. As you recall he developed chills, fever, chest pain and a cough productive of brown sputum.

Dr. Harford, what lesion is usually associated with such a history?

Dr. CARL G. HARFORD: Pneumonia.

Dr. WOOD: The story certainly suggests acute bacterial pneumonia. Can you tell us, Dr. Harford, something of the effects of immersion on pulmonary infection in general? What happens when a patient takes in a large amount of water as this patient apparently did?

Dr. HARFORD: I have been interested in the effects of fluid on the susceptibility of the lung to infection by the pneumococcus. Very likely when this man fell into the water and "swallowed" a large amount some of it gained access to his trachea and bronchi. Most of the organisms which cause pneumonia, particularly the gram-positive cocci, are non-motile. Their transport, therefore, in the lung depends on the presence of fluid. The importance of edematous fluid in causing the spread of experimental pneumococcal pneumonia is well established. It is by way of edematous fluid that the pneumococci are carried not only from one bronchus to another but from alveolus to alveolus. This patient, who had chronic bronchitis, certainly harbored numerous bacteria in his pulmonary tree and these were undoubtedly spread to a number of areas in his lungs by the aspirated water. At some of these sites the organisms multiplied and widespread infection resulted.

Dr. WOOD: Another important point in the history is that this patient stood in the river for an hour in the cold water and then stood out in the rain for another hour before he was taken to his home. Dr. Smith, what

is the effect of chilling in such a situation as this? Is external chilling of importance in the pathogenesis of acute pulmonary infection?

Dr. RALPH O. SMITH: It has been shown in experimental animals that chilling increases susceptibility to pneumonia. Certainly patients frequently give a history of having been chilled prior to the onset of respiratory infection. The phenomenon is probably associated with vasoconstriction or with the effect that chilling has on the mucous membranes of the bronchi *per se*.

Dr. WOOD: Nungester at the University of Michigan studied the effect of chilling on experimental pulmonary infection in rats. He introduced pathogenic organisms into the upper respiratory tract of animals and then exposed them to low temperatures. The incidence of pneumonia in animals so chilled was significantly higher than in animals who had not been subjected to low temperature. Dr. Nungester presented evidence that chilling slows the epiglottis reflex which normally prevents the infected mucus of the nasopharynx from entering the trachea.

Dr. HARFORD: Many years ago Dr. Goldman carried out some interesting experiments on the influence of chilling in human beings.

Dr. WOOD: Yes, Dr. Goldman, in conjunction with Dr. Samuel Grant and Dr. Stuart Mudd, who is now Professor of Bacteriology at the University of Pennsylvania, undertook these experiments while they were medical students in this School. Dr. Goldman, would you tell us about this work.

Dr. GOLDMAN: We were told by one of our instructors in pathology that chilling of the body resulted in congestion of all the organs. We were skeptical regarding his statement and attempted to examine its validity. We first determined the temperatures of mucous membranes in the nose, throat, pharynx and larynx with a thermocouple. After these control observations we entered an icebox and chilled ourselves as thoroughly as possible. Following chilling,

we found that ischemia rather than congestion developed in the upper respiratory tract and we usually developed sinusitis, laryngitis, pneumonitis or pleurisy within a few days after exposure. We also studied the bacterial flora of the mucous membranes and found that streptococci, for example, would persist after chilling longer than many of the other common inhabitants of the respiratory tract. We concluded that ischemia lowered the resistance of the mucous membranes and allowed pathogenic bacteria to flourish.

DR. WOOD: It seems quite clear then that this patient had pneumonia. The final phase of his illness began after he was admitted to the hospital and it was discovered that he had early empyema. The fluid removed from his chest was thin at the time of the first thoracentesis but subsequently became very thick and *B. proteus* and coliform organisms were cultured from the fluid. Furthermore, a rather large amount of air was withdrawn at the time of the second thoracentesis. Dr. Goldman, would you comment on the development of the empyema.

DR. GOLDMAN: It seems likely that this patient had a mixed pulmonary infection from the beginning and that empyema developed in one of two ways: either by direct extension of the infection to the pleura such as is common in pneumococcal pneumonia or by abscess formation and subsequent rupture of the abscess directly into the pleural cavity with the development of a fistula. In view of the fact that the patient brought up a cupful of brownish sputum very early in the course of his acute illness it would seem likely that the pneumonic process was a necrotizing one and probably extended into the pleural cavity directly. The presence of so much air suggests a bronchopleural fistula.

DR. WOOD: The organisms that were grown from the empyema fluid, Dr. Harford, were not those commonly identified as etiologic factors in pneumonia. How do you explain their presence in the pleural cavity?

DR. HARFORD: *B. proteus* is a common contaminant. Despite rigid technical precautions the possibility of a contaminated culture must be considered.

DR. WOOD: *Proteus* was also recovered in the sputum and it would seem unlikely, would it not, that both cultures could have been contaminated? Furthermore, the fluid was foul, as it occurs in empyema, due to coliform organisms. Dr. Flance, would you be inclined to consider the possibility of suppuration close to the pleura with subsequent rupture of an abscess as the cause of the empyema?

DR. FLANCE: That explanation seems to me to be the most logical. It is conceivable that the patient originally had a very small opening into the pleural space which subsequently was widened.

DR. WOOD: Also an abscess may rupture into the pleural space and the defect close promptly. In such instances empyema without a demonstrable fistula results.

DR. WILLIAM DAILY: I should like to suggest that this patient had arteriosclerotic heart disease with congestive failure. A rather chronic cough, edema and the subsequent finding of pleural effusion are all consistent with this suggestion.

DR. WOOD: I was just about to ask Dr. John Smith whether he thought this patient had significant coronary artery disease and whether at any time he had cardiac failure.

DR. JOHN R. SMITH: Certainly this patient may have had sclerotic coronary arteries but I did not think that his early edema was due to cardiac failure. Patients in this age group often exhibit some ankle edema after prolonged standing. It is conceivable that following development of the severe infection cardiac failure ensued as a complication.

DR. WOOD: Why was edema noted over the site of the thoracic lesion?

DR. J. R. SMITH: The patient probably lay on that side in order to relieve his chest pain and the edema may have developed because of the dependence of that region.

DR. WOOD: Patients with pneumonia usually lie on their affected side and edema

is not uncommonly localized because of position.

Dr. HENRY A. SCHROEDER: An alternate suggestion in regard to terminal edema is that it was of renal origin. The patient's blood pressure was low and remained low, and it is conceivable that there was enough decrease in renal blood flow to give rise to edema.

Dr. WOOD: There are two other points which we shall not have time to discuss adequately, but I think that we should mention them in passing: First, the patient had a mean corpuscular volume of 115. Dr. Moore, would you comment on this finding?

Dr. CARL V. MOORE: I see no apparent reason for that result.

Dr. WOOD: Further, the patient's blood calcium was 8 mg. per cent. What about that, Dr. Wade?

Dr. LEO J. WADE: The phosphorus was slightly elevated although certainly not enough to explain the low calcium.

Dr. WOOD: In summary then, we believe that at postmortem examination the findings in this patient will include emphysema, chronic bronchitis, probably with bronchiectasis, acute pneumonia and empyema, possibly as a result of rupture directly into the pleural cavity of an area of pulmonary suppuration. Furthermore, there may be a significant degree of coronary sclerosis and, although not likely, a bronchogenic carcinoma may possibly be present.

Clinical Diagnosis: Acute bacterial pneumonia with empyema (? following rupture of abscess); emphysema; chronic bronchitis; bronchiectasis; ? coronary artery sclerosis; ? bronchogenic carcinoma.

PATHOLOGIC DISCUSSION

Dr. ELLIS J. VAN SLYCK: At autopsy the body was that of a well developed, poorly nourished, elderly white male. There was moderate pitting edema of the ankles, legs, thighs and scrotum.

Upon opening the thorax 400 cc. of thin, blood-tinged fluid were seen to be present

in the right pleural cavity. The left pleural space was the site of a loculated empyema cavity; a thick fibrinous exudate covered the left lung and divided the cavity into several pockets, from which a total of 700 cc. of thick, green, foul-smelling pus were evacuated.

In the lateral aspect of the left lower lobe just beneath the pleura there was a lesion, roughly 5 cm. in diameter, which consisted of black, semisolid, necrotic material which communicated with one of the larger empyema pockets through the perforated visceral pleura. Surrounding this involved area the lung parenchyma was firm, and blood-tinged edematous fluid exuded from the cut surface. Two firm, grey-yellow raised nodules of lung tissue, about 3 cm. in diameter, were seen superimposed on the congested and edematous parenchyma of the left lower lobe. In this same region numerous small thrombi were present in the tertiary branches of the pulmonary artery. Other changes in the lungs were (1) white, firm, stellate scars at both apices; (2) 1 mm. calcified nodules in the parenchyma of the right upper lobe; (3) a calcified nodule, measuring 1 cm. in diameter in the upper portion of the right lower lobe; (4) generalized slight emphysema of the senile type. The mediastinal lymph nodes were moderately enlarged and cut with increased resistance.

The pericardial sac contained 10 cc. of clear yellow fluid. Scanty fibrinous exudate was present on the epicardial surface; it could be removed with ease. The heart weighed 320 Gm., and the outstanding pathologic lesion was found in the coronary arteries where generalized thickening of the walls and narrowing of the lumina was widespread. In the left anterior descending branch a calcified plaque or thrombus, about 1.5 cm. in length, was seen to occlude the lumen completely about 1 cm. from the ostium. The right coronary artery was hypoplastic and failed to establish its normal anastomosis with the circumflex branch of the left coronary. The endocardium of the left ventricle overlying the

septum contained an area, 2 cm. in diameter, which was white and thickened. Patchy streaks of fibrosis were seen in the musculature of the septum. Other findings referable to the heart were moderate sclerotic changes in the aorta, aortic and mitral valves and a duplication of a cusp of the pulmonary valve.

The peritoneal cavity contained 100 cc. of clear yellow fluid. The stomach was remarkable in that the mid-point of the lesser curvature, a polypoid, fungating mass about 10 cm. in diameter, was noted. It was soft, multilobulated, greyish-green in color and on its cut surface several areas of hemorrhage and liquefaction were seen. Extension of the tumor in the subserosal lymphatics was evidenced by the raised white streaks which were visible through the serosa. A large mass of matted lymph nodes, 0.8 by 3 by 3 cm., surrounded the body of the pancreas and included the lesser omentum. When these nodes were sectioned, tan colored, semisolid material oozed forth in some regions; other nodes showed complete replacement of lymphoid tissue by soft white tissue which appeared to be malignant.

Around the abdominal aorta of the level of the renal arteries there was another large conglomerate group of nodes which also appeared to be the site of metastatic growth. The renal vessels were neither occluded nor invaded by metastatic tissue. The liver was likewise free from metastases.

DR. R. A. MOORE: On the basis of the gross examination it is apparent that the pathologic changes fall into three categories, namely; pulmonary, cardiovascular and gastrointestinal. As far as the pulmonary lesions are concerned the gross appearance is certainly that of pneumonia of the necrotizing variety associated with the formation of an abscess in the periphery of the lung and subsequent rupture into the pleural cavity with formation of empyema. Loculation of the empyema cavity was apparent. In regard to the coronary disease there was moderately advanced arteriosclerosis of the major vessels. The heart

which weighed 320 Gm. was probably not grossly enlarged, but there was total occlusion of the descending left coronary artery with an old infarct in the septum. Associated evidence of cardiac disease was the finding of 400 cc. of fluid in the right pleural cavity, 100 cc. in the peritoneal cavity, some edema of the lower extremities and chronic passive congestion of some of the viscera. All of these observations indicate that this patient had some element of cardiac failure. A culture of the fluid in the right pleural cavity remained sterile and thus was not the result of the bacterial infection which affected the left lung and pleural space. Arteriolar sclerosis of the kidneys, that is, nephrosclerosis—was present to a moderate extent.

The lesion in the stomach was identified grossly as a carcinoma of the polypoid type; there were metastases to all of the regional lymph nodes but none to the lungs or liver.

One problem in connection with the infection in the lung is presented. There were thrombi in the tertiary branches of the pulmonary arteries in the involved area, and the possibility that the process represented an infected infarct or an infarct with surrounding pneumonia and subsequent liquefaction and abscess formation must be considered. Grossly, all of the evidence pointed to primary pneumonia, but gross examination *per se* is not sufficient to enable us to exclude occlusion of vessels as a factor in the development of the lesion.

If we turn to the microscopic findings, Figure 1 is a characteristic section of the lung in the region of the abscess. There is total necrosis of pulmonary tissue. The pneumonia is characterized by the presence of a moderate to large amount of fibrin and cells, many of which have undergone karyorrhexis scattered throughout the pulmonary alveoli. The next section (Fig. 2) is a higher power view of the same area and the character of the cells may be seen. There are both mononuclear and polymorphonuclear leukocytes, many of which are undergoing necrosis. This lesion must be considered as an example of a necrotizing

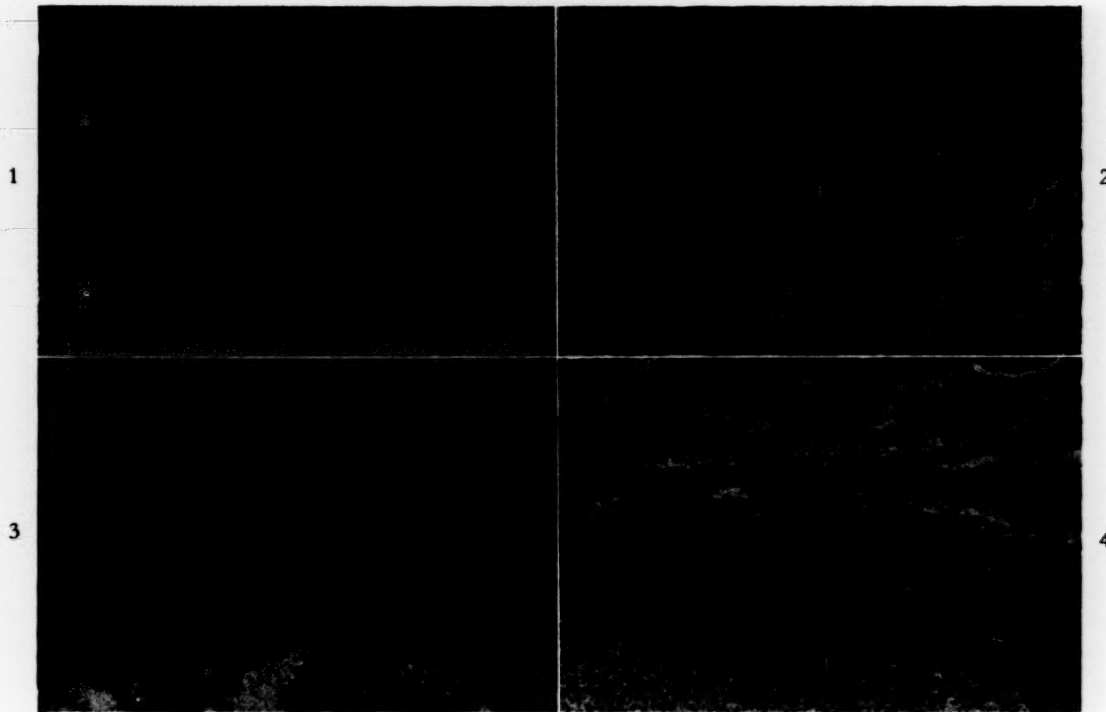


FIG. 1. Section of the lung in the area of necrotizing pneumonia.

FIG. 2. Higher power view of the lesion showing the cellular exudate.

FIG. 3. Oil immersion photomicrograph of a section stained for bacteria; both cocci and bacilli are present.

FIG. 4. Section showing a thrombus in one of the pulmonary arteries.

inflammatory process. In at least one area the alveolar wall has been involved by necrosis and an abscess has been produced. In Figure 3 a photomicrograph of bacteria is shown; in the lesion both gram-positive cocci and gram-negative bacilli are present, some of which have been phagocytized while others are free in the exudate. No culture was made from the lung; a culture of the empyema fluid was reported as yielding hemolytic staphylococcus aureus, a few colonies of a non-specific klebsiella, *Pseudomonas aeruginosa*, a few *Aerobacter aerogenes*, alpha hemolytic streptococci and a few diphtheroids. In attempting to evaluate the bacteriologic findings and to determine the organism or organisms responsible for the pneumonia, the most likely conclusion is that the hemolytic staphylococci plus one of the gram-negative bacilli were probably of major importance.

Figure 4 is a section of one of the pulmonary artery thrombi. The vessel wall may be seen with surrounding lung tissue above

and the thrombus below. Although there is exudate in the alveoli, there is neither an inflammatory reaction within the thrombus nor an increase in cells. Likewise, there is no inflammatory reaction in the vessel wall. I think, therefore, that when one considers the gross and the microscopic findings, he may reject the postulate that this lesion is an example of an abscess resulting from an infarct and instead may accept it as pneumonia which has progressed to necrosis and extension through the pleura. The next section (Fig. 5) bears on the duration of the disease in relation to the diagnoses of bronchitis and bronchiectasis. Although the pleura itself is not thickened, there is a fibrinous exudate on its surface without adhesions and without organization. Thus, the pleurisy is of very recent origin. We were unable to identify dilated bronchi at the time of autopsy; however, I thoroughly agree with Dr. Goldman that the change in a bronchus from the normal to the bronchiectatic state is a gradual one and

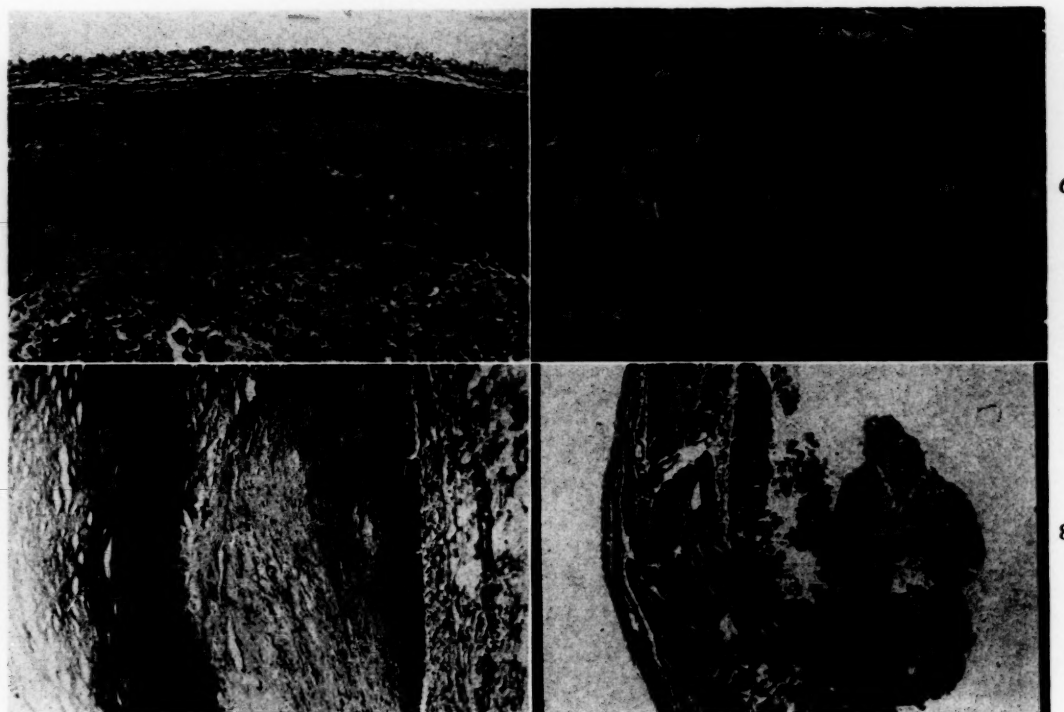


FIG. 5. Section of the pleural wall showing unorganized fibrinous exudate.

FIG. 6. A silicotic tracheobronchial lymph node.

FIG. 7. Section of the anterior descending branch of the left coronary artery showing an arteriosclerotic plaque which obliterates the lumen.

FIG. 8. Low power view of the polypoid carcinoma of the stomach.

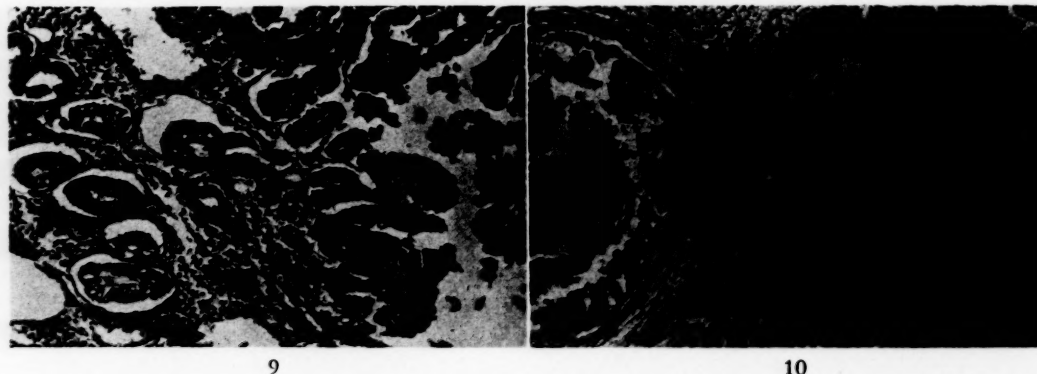


FIG. 9. A higher power view showing the junction of normal and carcinomatous glands in the stomach wall.

FIG. 10. Metastatic carcinoma in a periaortic lymph node.

there is a period during the change when the pathologist is unable to make a definitive diagnosis. The explanation of the patient's four-year history of cough is not apparent to me. In the tracheobronchial lymph nodes (Fig. 6) and to a limited extent in the lungs there are typical silicotic nodules. Looking at these sections, without regard for the history, I would not be impressed with the amount of anthra-

cosilicosis but conceivably it may have played a part in his chronic cough.

Figure 7 is a section of the anterior descending branch of the left coronary artery showing complete or almost complete obliteration of the lumen by an arteriosclerotic plaque containing calcium.

Figure 8 is from the stomach at the edge of the polypoid carcinoma which Dr. Van Slyck described. The transition from normal

mucosa to carcinoma is apparent. The next section (Fig. 9) is a higher power view from the junction of normal and carcinomatous glands. In Figure 10 the periaortic lymph nodes with metastatic carcinoma are seen.

In summary then, Dr. Wood, this man had a recent necrotizing pneumonia with abscess and empyema and pulmonary artery thrombi secondary to the inflammatory process. He also had some cardiac failure, probably on the basis of severe arteriosclerosis of the coronary arteries and an old infarct; finally, there was carcinoma of the stomach with lymph node metastases which probably accounted for the weight loss and anemia, the cause of which was not totally clear clinically.

DR. WOOD: This is a most instructive case for it illustrates that carcinoma of the stomach can be completely silent. Dr. Carl Moore has just pointed out to me two leads in the laboratory data to which we should have paid attention: First, there was more anemia than could be accounted for

by the diagnoses which we made and in one smear there was a suggestion of hypochromia. Later data in regard to the hypochromia were, however, conflicting. Second, one of the stool examinations was positive for occult blood.

Final Anatomic Diagnoses: Necrotizing bronchopneumonia in the lower lobe of the left lung with liquefaction and rupture into the pleural cavity; organizing thrombi in the tertiary branches of the pulmonary artery to the lower lobe of the left lung adjacent to the pneumonia; loculated empyema, left (700 cc.); arteriosclerosis of the coronary arteries, advanced in the left descending coronary artery with occlusion, and of the left circumflex and right coronary arteries, moderate; healed infarct in the anterior myocardial septum; polypoid carcinoma of the lesser curvature of the stomach; metastatic carcinoma in the lymphatics of the serosa of the stomach and the lesser omental, peripancreatic and periaortic lymph nodes about the renal arteries.

Special Feature

Western Society for Clinical Research

SECOND ANNUAL MEETING HELD IN LOS ANGELES, OCTOBER 22 AND 23, 1948

NEUROHUMORAL CONTROL OF HYPOPHYSIAL FUNCTIONS. *Harry B. Friedgood, M.D., Los Angeles, California.* (From the University of California.)

Parenteral administration of the adrenergic substance, neosynephrine, induced pseudo-pregnancy in 50 per cent of thirty-eight rats. This gonadotropic reaction of the rat's adeno-hypophysis was elicited also by electrical excitation of the cervix uteri in 73 per cent of sixty-two control experiments, in 84 per cent of thirty-two experiments after bilateral transection of the cervical sympathetic trunks and in 47 per cent of eighty-four experiments after bilateral superior cervical sympathetic ganglionectomy. These observations, in addition to data derived from previous experiments, constitute evidence for the existence of a neurohumoral adrenergic mechanism which controls the gonadotropic activity of the rat's adeno-hypophysis. Other evidence, stemming mainly from well established anatomic studies of the hypothalamic nuclei and of the angio-architecture of the hypothalamo-hypophysial area, suggests that the hypophysis cerebri is under dual neurohumoral control, viz., an adrenergic element regulates the function of the pars distalis of the adeno-hypophysis, and a cholinergic effect is exercised over the adeno-hypophysis and neurohypophysis. It is postulated that these adrenergic and cholinergic agents are secreted by the hypothalamus, neurohypophysis and proximal portions of the adeno-hypophysis (e.g., pars tuberalis) from whence they are carried via the hypophysial portal circulation to the pars distalis.

The foregoing considerations account satisfactorily on a neuro-anatomic and neurophysiologic basis for those endocrine disorders which are known to be associated with and apparently precipitated by emotional conflicts.

IS THERE A PULMONARY FACTOR IN THE PRODUCTION OF CYANOSIS IN CONGENITAL HEART DISEASE? *Arthur Selzer, M.D., San Francisco, California.* (From Stanford University.)

Blalock and Taussig and other authors have recently emphasized the importance of inadequate circulation or inadequate blood supply to

the lungs in the production of chronic cyanosis in congenital heart disease. Physiologically, the important question in the pathogenesis of chronic cyanosis is whether low arterial oxygen saturation is due to admixture of venous blood shunted from the right side of the heart into the arterial system or due to defective oxygenation of blood in the lungs.

This problem is approached from the pathologic standpoint, by an analysis of over 150 autopsied cases of congenital heart disease. In almost all cases clinically associated with cyanosis findings suggested a right-to-left intracardiac blood shunt. The most convincing evidence of the role which a venoarterial shunt plays in the pathogenesis of cyanosis is an analysis of cases of pulmonary stenosis with closed interventricular septum. It is shown that cyanosis is present if a patent foramen ovale offers a path for intracardiac shunt and is absent if the foramen is closed. The degree of cyanosis is related to the size of the foramen.

No direct or indirect evidence has been found for defective or incomplete pulmonary oxygenation. The beneficial effect of the Blalock-Taussig operation is best explained on the basis of recirculation of poorly oxygenated arterial blood through the lungs.

It is concluded that venous arterial blood shunt is the principal cause of chronic cyanosis in congenital heart disease. There is no known pulmonary factor in its production and the terminology of inadequate blood supply to the lungs is misleading and should be abandoned.

THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN HUMAN ARTERIAL HYPERTENSION. CARDIAC OUTPUT STUDIES IN DIFFERENTIAL SPINAL BLOCK. *Sidney S. Sobin, M.D., Los Angeles, California.*

Of the cardiovascular factors concerned in regulation of blood pressure the abnormality in human hypertension is believed to be an increased total peripheral resistance (TPR). Since TPR cannot be measured directly and is related to arterial pressure and cardiac output as defined by the equation $R = \frac{P_m \times 1332}{C.O.}$

dynes cm.⁻⁵ sec., measurement of these latter

two parameters provides TPR. Cardiac output was determined by the ballistocardiograph (Nickerson) and blood pressure by sphygmomanometer in eight hypertensive and three normotensive individuals under basal conditions and in various stages of sympathectomy produced by differential spinal block. Blood pressure fell in hypertensive patients but remained constant in normotensives despite similar degrees of sympathetic block. Concomitant with the fall in blood pressure in the hypertensives there was a striking increase in cardiac output and a marked fall in peripheral resistance. The course of events following the initial fall in blood pressure with the increase in cardiac output and decrease in peripheral resistance varied somewhat in different patients.

It is suggested that the increased cardiac output resulted from arteriolar dilatation and increased vis-a-tergo of venous return and that this may indicate tonic activity of the sympathetic nervous system in maintenance of the elevated blood pressure in human hypertension.

EFFECT OF ARTERIAL INSUFFICIENCY ON THE CIRCULATION RATE AND THE VOLUME INCREASE RATE OF THE EXTREMITY.
Travis Winsor, M.D., Los Angeles, California. (From the Nash Cardiovascular Foundation of the Hospital of the Good Samaritan.)

Studies on normal individuals and patients with vascular disease have shown definite differences in the time required for an increase to appear in the volume of the digit after partial emptying of blood from the peripheral vascular tree. An awareness of magnitudes of these differences occasionally gives insight into the extent and type of vascular diseases which may be present. The variations and types of response in individuals with different types of vascular disease indicate that this measurement may have merit under certain circumstances. It is the purpose of this report to describe a method for determining an extremity circulation time, an extremity circulation rate and a volume increase rate employing the plethysmographic technic, to present normal values for the extremity circulation time, extremity circulation rate and digital volume increase rate and to show deviations from the normal among patients with various degrees of arterial insufficiency.

From the procedures outlined retarded circulation rates and volume increase rates ordinarily indicate organic disease, whereas normal circu-

lation rates and retarded volume increase rates indicate organic disease or vasospasm. It is believed that these measurements may aid in gaining insight into the type and extent of vascular disease which may be present. Further study is necessary to evaluate the influence of edema, sympatholytic procedures, hypertension and alterations in tissue distensibility.

STUDY OF THE RATE OF DISAPPEARANCE OF A DIGITALIS GLYCOSIDE (LANATOSIDE C) FROM THE BLOOD OF MAN.
Meyer Friedman, M.D. and (by invitation) Rene Bine, M.D., San Francisco, California. (From the Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital.)

By means of the embryonic duck heart preparation it was found possible for the first time to determine the concentration of digitalis glycoside (Lanatoside C) in the sera of patients at various intervals of time after they had received the glycoside by vein.

It was found that the average concentration of glycoside in the ten patients studied was 0.25 microgram per cc. of serum immediately after the intravenous injection of 1.6 mg. of Lanatoside C. Seven and one-half minutes after injection the average concentration was 0.10 microgram per cc. of serum. At the end of fifteen minutes no glycoside could be detected in two of the ten patients and the average concentration in the remaining eight patients was 0.07 microgram per cc. of serum. At the end of thirty minutes glycoside (0.05 microgram per cc.) was detected in only one of the ten patients. No glycoside could be detected in any patient one hour after its injection.

These results indicate that after intravenous injection of a digitalizing dose of the particular glycoside employed (Lanatoside C) a very rapid disappearance of the drug from the blood stream occurs.

A QUANTITATIVE STUDY OF ATHEROSCLEROSIS.
Alvin J. Cox, M.D., San Francisco, California. (From Stanford University.)

Dehydration and extraction of 220 human aortas removed at autopsy yielded amounts of fatty material which were related to the age and sex of the corresponding patients. Comparison of different groups of the aortas shows more aortic lipid from those with hypertension and diabetes than from others without these conditions. There is little evidence of a significant effect of diet upon the amount of aortic lipid

although poorly nourished and alcoholic individuals had aortas containing slightly less lipid than the controls.

THE ROLE OF LIPOID METABOLISM IN PRODUCTION OF CORONARY ARTERIOSCLEROSIS AND ATHEROSCLEROSIS. *Lester M. Morrison, M.D., Albert L. Chaney, Ph.D., (by invitation) Lillian Hall, M.D. and (by invitation) William Gonzalez, M.D., Los Angeles, California.* (From the Los Angeles County General Hospital and the Department of Internal Medicine, Medical School of the College of Medical Evangelists.)

The effect of choline on the prevention of experimental cholesterol atherosclerosis: The oral feeding of 0.5 Gm. choline chloride daily, together with 0.5 Gm. cholesterol to twenty-nine, three-month old rabbits prevented atherosclerosis in 55 per cent of the animals at the expiration of the ninety-second-day experimental period. The oral feeding of 1.0 Gm. choline chloride daily together with 0.5 Gm. cholesterol to thirty-two three-month old rabbits prevented atherosclerosis in 78 per cent at the expiration of the ninety-second-day experimental period.

Absorption of aortic atherosclerosis by choline feeding: Choline caused re-absorption of aortic atherosclerosis in the majority of rabbits with lesions produced by cholesterol feeding.

Effect of blood cholesterol disorders on the coronary arteries and aorta: A series of 600 patients with diseases characterized by hypercholesterolemia and hypocholesterolemia during life was studied in relationship to coronary artery arteriosclerosis and aortic atherosclerosis as found at autopsy. These patients were compared to "controls" or patients in a series of deaths from sudden, acute illness (medical or surgical) and to a series of patients who died of chronic illnesses other than those of the other groups described. Patients who died of chronic diabetes mellitus, a disease characterized by hypercholesterolemia, showed a marked increase in coronary arteriosclerosis and aortic atherosclerosis as compared to a series of control patients who died of an acute illness and a series of control patients who died of chronic illnesses and a series of deaths from cancerous illnesses. Patients who died of chronic thyrotoxicosis, a disease characterized by hypocholesterolemia, showed a marked decrease in incidence of

coronary arteriosclerosis and aortic atherosclerosis as compared to the control series and all other groups described herein.

Cholesterol content of the coronary arteries and blood in acute coronary thrombosis: The average cholesterol content of the coronary arteries in a series of patients who died from an acute coronary artery thrombosis was analyzed biochemically and found to be four times as great as the average cholesterol content of the coronary arteries in a comparable group of control patients. Hypercholesterolemia was found (average value) in the group of patients who died of acute coronary artery thrombosis as compared to a normal blood cholesterol average in the comparable control group.

Changes in the blood cholesterol levels following one year of choline therapy in patients with acute coronary thrombosis: In summary, in a series of thirty-two normal subjects the constancy of blood serum cholesterol levels was re-affirmed over prolonged test periods using a modification of the Sperry-Schoenheimer serum cholesterol procedure. Wide variations in serum cholesterol values were found in a group of thirty-one patients with miscellaneous diseases. Marked fluctuations in serum cholesterol values were observed in a series of fifty patients who had recently experienced a coronary artery thrombosis. Analogous wide fluctuations in serum cholesterol values were found in a series of forty-eight patients who had recently experienced a coronary artery thrombosis and ingested 6 Gm. of choline daily. These fluctuations rendered it impracticable to determine whether choline effected a reduction or increase in serum cholesterol levels. It is suggested that variations in serum cholesterol exceeding 15 per cent when determined by the Sperry-Schoenheimer procedure or a proven modification thereof in an individual presumed to be normal may possibly indicate a systemic disorder or latent illness.

QUANTITATIVE ESTIMATION OF ALBUMIN, GAMMA GLOBULIN AND BETA-1 GLOBULIN IN HUMAN BODY FLUIDS BY IMMUNOLOGIC TECHNIQUES. *B. V. Jager, M.D. and (by invitation) Margaret Nickerson, Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

Antisera to highly purified serum albumin and to human serum gamma globulin and to a beta-1 globulin (Fraction IV-7-4) have been

prepared in rabbits. Employing quantitative precipitin technic, the amounts of proteins reacting to these antisera have been determined, using whole human serum and spinal fluid as antigens. For human serum antigens the immunologically estimated serum albumin is in close agreement with the electrophoretic estimation. For human serum gamma globulin the immunologic values are far in excess of electrophoretic estimations of gamma globulin. The reactive antigen in human serum to iv-7-4 antiserum comprised approximately 3 per cent of the total serum protein in blood from three normal subjects. In spinal fluids the values for serum albumin and serum gamma globulin were in agreement with the values obtained by Kabat and co-workers (1948). Certain theoretical and practical limitations of the quantitative precipitin technic are considered.

ELECTROPHORETIC STUDIES OF SERUM MUCOPROTEINS. *John W. Mehl, M.D., Jane Humphrey, (by invitation) Florence Golden, (by invitation) and Richard J. Winzler, Los Angeles, California.* (From the Los Angeles County General Hospital and the Department of Bio-chemistry and Nutrition, University of Southern California School of Medicine.)

Previous studies have shown that an increased amount of "protease" appears in the plasma or serum of patients with neoplastic and infectious diseases. Previous investigations of this material have shown that it is a mucoprotein.

Electrophoretic studies of this mucoprotein isolated from normal human plasma by chemical procedures show that it is present in the α_1 -globulin fraction at pH 8.4. Studies of the mobility as a function of pH have shown that it is heterogeneous but that all of the components have an isoelectric point below that of the other normal serum proteins. These studies indicated that a pH of 4.5 would be most advantageous for the demonstration of these mucoproteins by direct electrophoretic studies of serum since at this pH all other normal serum proteins would be positively charged.

The electrophoretic study of normal serum has shown that there are two components which are still negatively charged at pH 4.5. These two components are increased, but not always in the same proportions, in conditions in which the mucoprotein determined by chemical means is increased. One of these components has been

isolated by electrophoresis from pathologic serum and found to have essentially the same chemical properties as the material prepared by precipitation from normal serum. Both of the components which are elevated in pathologic sera may be increased by adding the mucoprotein precipitated from normal serum.

EFFECT OF PARENTERAL BOVINE ALBUMIN INJECTIONS ON EXCRETION OF HEMOGLOBIN IN THE RAT. *Richard W. Lippman, M.D. (introduced by David Ryland, M.D.), Los Angeles, California.* (From the Institute for Medical Research, Cedars of Lebanon Hospital.)

Addis and his associates have shown that massive proteinuria may be induced in rats by the parenteral injection of bovine albumin and other proteins. This study was made to analyze the proteinuria with respect to the factors of filtration and re-absorption through the use of hemoglobin as an indicator protein.

Animals received an intravenous injection of hemoglobin at the height of proteinuria produced by the injection of bovine albumin intraperitoneally. Serum concentrations of hemoglobin and the excretion rate of hemoglobin were measured. Control animals received intraperitoneal injections of 0.85 per cent sodium chloride solution. The animals who received albumin excreted hemoglobin at double the rate of the controls. In addition the serum concentration threshold for hemoglobinuria was reduced from 75 mg. per 100 cc. to less than 25 mg. per 100 cc. These results were interpreted to indicate both diminished tubular re-absorption of protein and increased glomerular permeability to protein in experimental animals.

METABOLISM OF ENDOGENOUS AND EXOGENOUS ANDROGENS BY PATIENTS WITH LIVER DISEASE. *Laurance W. Kinsell, M.D. and Maxine E. Hutchin (by invitation), Sheldon Margen, M.D., San Francisco and Oakland, California.* (From the Division of Medicine, University of California Medical School and Department of Medicine, U. S. Naval Hospital.)

Reports by a number of clinicians and investigators indicate that the liver normally plays a major role in the metabolism of steroid hormones. It has also been suggested that certain

endocrine abnormalities noted in some patients with acute and chronic liver damage are referable to malmetabolism of endogenous steroids.

In an effort to evaluate the preceding observations a large group of patients with acute and chronic liver damage have received testosterone propionate and free testosterone and have been followed from the standpoint of 17-ketosteroid excretion prior to, during and following administration of testosterone. The results so obtained have been compared with similar studies in normal individuals.

In general it has been found that only those patients with considerable hepatic impairment show a significant abnormality in their ability to metabolize administered androgens to the physiologically less active compounds which are excreted as neutral 17-ketosteroids.

In a large group of patients with acute and chronic liver disease gynecomastia has been found to be a rare occurrence and to occur more commonly during convalescence than during the more severe phases of the disease. It is also the strong impression of the authors that in the rank and file of cirrhotic patients the loss of axillary and pubic hair and other endocrine abnormalities occur with only slightly greater frequency than is the case in a comparable group of patients who present an equal degree of debility from non-hepatic causes.

EFFECTS OF DESOXYCORTICOSTERONE IN RELATION TO ANTIDIURETIC FACTOR EXCRETION. *Julia Goodsell Skahen (by invitation) and D. M. Green, M.D., Seattle, Washington.* (From the University of Washington School of Medicine.)

Subcutaneous implantation of desoxycorticosterone in rats is followed by a prompt rise in fluid intake and subsequent elevation of blood pressure to hypertensive levels. Since upward disturbances in water balance presumably invoke responses by the posterior pituitary, studies were made of the effect of desoxycorticosterone on antidiuretic factor excretion and its relationship to changes in blood pressure.

Results indicated that the implantation of DCA pellets was followed both by hypertension and by increased antidiuretic factor excretion. However, the substitution of saline solution for drinking water in rats given no desoxycorticosterone also produced a rise in antidiuretic factor excretion but did not cause blood pressure elevation. In general, antidiuretic factor output appeared correlated with increased fluid intake,

regardless of the means used to stimulate a rise in voluntary fluid consumption.

The excretion of antidiuretic factor following desoxycorticosterone administration appeared to be a response to the drug-induced disturbance in fluid balance. No immediate relationship to the development of hypertension was demonstrated.

URINARY COPROPORPHYRIN EXCRETION IN PATIENTS WITH NEOPLASTIC DISEASES. *Howard R. Bierman, M.D., Louis A. Strait (by invitation) and M. Rhenoff (by invitation), San Francisco, California.* (From the Laboratory of Experimental Oncology, University of California Medical School.)

The twenty-four hour urinary coproporphyrin excretion has been studied in patients suffering from various neoplastic diseases. There appears to be a cyclic increase in excretion of coproporphyrin well beyond the present accepted limits of normal at regular periods in some patients who have been studied continuously for two to three months.

In eleven of sixteen instances administration of HN_2 in doses from 0.1 to 0.6 mg./Kg. body weight was followed by varying increases in coproporphyrin excretion over the pretreatment levels within twenty-four to ninety-six hours. There appears to be no relationship to the urinary volume.

Repeated daily doses of HN_2 in one patient exhausted the mechanism for increased coproporphyrin excretion after nine days.

Hematopoietic regeneration may be responsible for the coproporphyrinuria in some cases since there appears to be no correlation with hematopoietic or neoplastic tissue destruction. The possibility of an underlying neoplastic host mechanism may account for the periodic increase in coproporphyrin excretion unrelated to therapy.

LYMPHANGIOGRAPHY IN THE DIAGNOSIS OF CHYLANGIOMA AND LYMPHEDEMA. A PRELIMINARY REPORT. *Norman E. Freeman, M.D., San Francisco, California.*

Chylangioma and chylous fistula are rare conditions. Knapper in 1928 collected twelve cases from the literature and described one case of his own. In his patient the chylous fistula of the popliteal space was closed one year after resection of the pelvic lymphatics. Two cases of this condition have been encountered, one on the service of I. S. Ravdin at the University of

Pennsylvania Hospital and the second on the Children's Service at the University of California Hospital. In the former, studies were made on the fat content of the chyle obtained by puncture of a vesicle on the scrotum at intervals following ingestion of cream. In the latter the lymphatics of the pelvis, external genitalia and lower extremities were visualized by x-ray after injection of diodrast by direct puncture of a vesicle on the labia majora. It was shown that the valves of the lymphatics were deficient in this case. In both patients an attempt was made to resect the pelvic lymphatics. Although there was temporary improvement, in neither case was the condition completely relieved. The possibility of lymphangiography in the study of lymphedema is discussed.

ON THE CLINICAL USEFULNESS OF HYPOTONIC INTRAVENOUS SOLUTIONS. *F. R. Schemm, M.D., John A. Layne, M.D. and (by invitation) John S. Gilson, M.D., Great Falls, Montana.* (From the Department of Medicine, Great Falls Clinic.)

We have found hypotonic solutions given by vein effective in maintaining water balance when the administration of water *per se* was indicated and when the customary amounts of sodium chloride or dextrose found in isotonic solutions appeared undesirable. The hypotonic solutions, at first of two-thirds and later of one-half of isotonic strength, were particularly useful in postoperative or azotemic diabetic patients with cardiovascular-renal complications.

Hypotonic solutions have now been used in more than thirty-five instances, extending over periods of treatment from five to thirteen days. A total of from 1 to 4 L. were given daily, in volumes varying from 500 to 1,500 cc. at a time, with a rate of flow that ranged from 14 to 22 cc. per minute. One of the most useful solutions contained 2.25 Gm. of sodium chloride and 12.5 Gm. of dextrose in 1,000 cc. of water. With this latter solution, one can give, for example, with 4,000 cc. of water 50 Gm. of dextrose and 9 Gm. of sodium chloride in twenty-four hours. These amounts give a good base line for maintenance in, for example, postoperative diabetics with duodenal drainage, providing enough water and dextrose and not too much sodium. One-half isotonic strength saline or dextrose can be added or substituted for the combined solution when there appears to be need for more sodium or dextrose.

Studies of the blood immediately after administration of these hypotonic solutions or after several days' use of them showed no detectable dilution or disturbance of the electrolyte pattern of the blood, indicating how swiftly plain water is diffused throughout the 50 L. of total body water. In some instances these solutions were used in patients recovering from episodes of acute, profuse pulmonary edema.

MYOTONIA DUE TO COLD. A BENIGN SYNDROME OF MYOTONIC CONTRACTION AFTER EXPOSURE TO COLD MANIFESTING A CHARACTERISTIC HEREDITARY PATTERN. *Frank H. Tyler, M.D., Thomas A. Witten, M.D. and Fayette B. Stephens, Ph.D., (by invitation and introduced by Hans H. Hecht, M.D.), Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

The disease (paramyotonia congenita) described by Eulenberg in 1886 and by Rich in 1895 has not been clearly distinguished from other myotonias by most neurologists since that time. The opportunity to study a family with the disorder now presents itself. The syndrome consists of myotonic reaction occurring most frequently in facial, oculomotor and intrinsic hand muscles as the result of exposure to cold. Other factors are of little importance in the occurrence of the myotonia, but quick movement following rest or gross voluntary movement occasionally precipitate it in certain members of the family. The anomaly is present at birth and persists throughout life with a tendency to improvement not very marked and without the development of muscular atrophy and other degenerative changes.

A case of myotonic muscular contraction induced by exposure to cold or chilling is reported. A family history of sixty-two persons manifesting the disorder with a typical Mendelian dominant pattern of inheritance is presented. The myotonia responds to quinine in the same fashion as other myotonias.

CLINICAL AND LABORATORY RELIABILITY OF PROTEIN-BOUND BLOOD IODINE DETERMINATIONS. *Donald W. Petit, M.D. (by invitation), Paul Starr, M.D. and A. L. Chaney, Ph. D. (by invitation), Los Angeles, California.* (From the Department of Medicine, University of Southern California.)

Because of increasing acceptance of the usefulness of protein-bound blood iodine determina-

tions as an index of thyroid function, it was decided to subject the procedure used here to clinical test. A "blind" technic was used to find: (1) the reproducibility of results from identical specimens; (2) effect of an ordinary meal; (3) effect of mild exercise; (4) effect of ingestion of inorganic and organic iodine compounds; (5) the role of serum proteins in the final level of protein-bound blood iodine.

Ninety per cent of 112 specimens drawn from fifty-one subjects and tested in duplicate or triplicate agreed within 3 gamma per cent. Similar technics used for the testing of seventy-one specimens drawn from five normal males revealed no significant change in protein-bound blood iodine after meals or after mild exercise.

Serial determinations of protein-bound blood iodine in three patients receiving inorganic iodine solution revealed unreliable results during the ingestion of iodine and for forty-eight to seventy-two hours after its cessation. Isolated determinations on five patients after cholecystography revealed elevated protein-bound iodines for as long as three months after the drug had been administered. Similar tests on four patients who had had iodized oil introduced into the lung or subarachnoid space showed elevated levels of protein-bound iodine for periods in excess of one year. The finding of low protein-bound iodine levels in patients with low serum protein and apparently normal thyroid function deserves further study.

FACTORS INFLUENCING THE EFFECTIVENESS OF RADIOIODOTHERAPEUSIS. *Robert H. Williams, M.D., Seattle, Washington.* (From the Department of Medicine, University of Washington School of Medicine.)

The results of radioiodotherapy in 106 patients with thyrotoxicosis were found to compare favorably with the results of treatment by antithyroid drugs and subtotal thyroidectomy in 195 subjects and with the results of antithyroid drugs administered for prolonged intervals to 119 individuals.

The main problem in radioiodine therapy is in determining the optimum dosage. Although some indication of the quantity of isotope concentrated in the thyroid can be determined by estimating the rate of excretion of the radioiodine in the urine or by epithyroid counts, there are apparently many factors influencing the ultimate results of therapy, especially when I^{131} is used. Although the total amount of isotope localized in the thyroid is important, its

distribution in the acini is significant and factors influencing the turnover of iodine are also important.

Studies were made of the influence on iodine metabolism of adrenalin, trauma, bacterial toxins, halides, food, environmental factors, thiocyanate, propylthiouracil, adrenalectomy and thyroidectomy. The results of these studies and their possible influence upon radioiodotherapy are available for presentation.

THE HEART IN INFECTION. *Irving Fine, M.D. (by invitation), Henry Brainerd, M.D. and Maurice Sokolow, M.D., San Francisco, California.* (From the University of California Medical School.)

Eighty-four patients selected as being free of pre-existing heart disease, who were suffering from a variety of acute infectious diseases, were studied intensively to determine the nature and incidence of resulting abnormalities of the heart. The patients were subjected to serial clinical observations, determinations of venous pressure and circulation time and standard and unipolar electrocardiograms. An attempt was made to correlate clinical and electrocardiographic findings.

Thirty-three and three-tenths per cent of patients studied demonstrated definite abnormalities of the electrocardiogram at some time in the course of infection. These patients were suffering from typhoid, diphtheria, meningitis due to meningococci, pneumococci and *H. influenzae*, pneumococcal pneumonia, acute streptococcal infections and mumps. The commonest electrocardiographic abnormality was alteration of the T waves, followed by prolonged P-R interval, prolonged Q-T interval, arrhythmias, disturbed intraventricular conduction and S-T segment abnormalities in descending order of frequency. Eighteen patients subjected to artificial fever therapy did not exhibit similar changes.

Alterations of intensity or quality of the mitral first sound occurred in 46.4 per cent of patients with myocarditis as contrasted to 3.7 per cent of patients without myocarditis; this finding had the highest correlation of various clinical observations with electrocardiographic changes. Gallop rhythm was noted in 28.5 per cent of patients with myocarditis and occurred transiently in 7.2 per cent of patients without electrocardiographic abnormalities. Systolic murmurs occurred in 42.8 per cent of abnormal hearts but were heard in 25.9 per cent of individuals without demonstrable myocarditis.

The circulation time was markedly decreased by fever but was abnormal in only two patients with myocarditis. One patient with myocarditis exhibited elevation of the venous pressure.

EFFECTS OF THE ADMINISTRATION OF STREPTOMYCIN IN TREATMENT OF EXPERIMENTAL OBSTRUCTIVE APPENDICITIS. *H. A. Davis, M.D., J. K. Burns, M.D., (by invitation) J. D. Schuler, M.D. (by invitation), T. E. Wade, M.D. (by invitation) and A. B. Webber, M.D., Los Angeles, California.* (From the Hunterian Laboratory, the Department of Surgery and the Graduate School of Medicine, College of Medical Evangelists.)

In a study reported elsewhere it was demonstrated that a standard type of injury to the vermiform appendix of rabbits (devascularization with obstruction of 7 cm. from the tip) caused death in 80 per cent of untreated rabbits.

In order to study the effect of streptomycin upon the mortality rate five groups of rabbits were studied. The standard form of injury to the appendix was produced in all groups. Streptomycin in a dose of 50 mg. twice daily was injected subcutaneously for fourteen days. Streptomycin definitely lowered the immediate mortality rate from experimental obstructive appendicitis in rabbits, especially when administration was started within twenty-four hours after the lesion in the appendix was produced. The critical period during which a sharp rise in mortality occurs is delayed in streptomycin-treated rabbits and lies between twenty-four and forty-eight hours.

The rabbits were allowed to survive for a period of three months following discontinuance of streptomycin therapy. The incidence of residual abscess formation was high. The abscesses were usually small and apparently did not interfere with the health or nutrition of the animals. In a small number of animals the abscesses were very large.

STUDIES OF PLASMA QUINIDIN CONTENT IN RELATION TO SINGLE DOSE ADMINISTRATION, TOXIC MANIFESTATIONS AND THERAPEUTIC EFFECT. *Richard W. Kalmensohn (by invitation) and John J. Sampson, M.D., San Francisco, California.* (From the Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital.)

The purpose of this work is to present (1) the quinidin plasma levels after single doses of the drug given by the intramuscular route as compared to the oral and rectal routes, (2) the plasma quinidin content when toxic manifestations are exhibited by patients receiving the drug and (3) the levels at which conversion of auricular fibrillation to sinus rhythm occurs.

A new compound, quinidin lactate, was administered intramuscularly to six patients with normal hearts, two in single doses of 0.13 Gm. and four in doses of 0.6 Gm. In the latter dosage (0.6 Gm.) the curve of rise and fall of quinidin plasma levels reached a maximum content of 1.76 to 3.45 mg. per L. between one and two and two-third hours and fell to 25 to 50 per cent of the maximum in four hours and to 10 to 25 per cent in ten to twelve hours, with a small residual present in twenty-four hours. This compared with previous reports and our own observations in six patients using single oral doses of 0.6 Gm. quinidin sulfate, namely, 2.9 to 3.7 maximum content in one-half to four and one-half hours with an average of two and one-fourth hours and retention of about the same fall in plasma content at twelve and twenty-four hours. Rectal administration of 0.6 Gm. quinidin sulfate resulted in maximum levels of 0.51 to 1.19 mg. per L. with only a trace remaining in twelve hours.

Of the sixteen patients receiving test doses of quinidin by various routes two instances of hypotension were noted and these occurred only in the (four) patients given 0.6 Gm. quinidin lactate intramuscularly with maximum plasma content under 4.0 mg. per L. In the two instances in which hypotension developed during oral therapeutic use of quinidin sulfate the plasma contents were higher, namely, 6.9 and 8.1 mg. per L. This implies that administration of quinidin intramuscularly, as has been suspected from previous experience with its intravenous use, for reasons undetermined carries a greater risk than from oral or rectal use.

In six of fourteen instances of oral quinidin administered therapeutically the quinidin content of the plasma at which the various toxic manifestations first appeared varied from (1) 0.63 to 10.8 mg. per L. with nausea (five cases), diarrhea (three cases) and giddiness (three cases); (2) 4.86 and 12.68 with headache (two cases); (3) 8.1 and 14.5 with diplopia (two cases); (4) 3.65 and 8.1 with scotomas (two cases); (5) 14.5 with deafness (one case) and (6) 6.9 and 8.1 with hypotension (two cases).

Whereas gastrointestinal symptoms were the commonest initial evidence of toxicity, they accompanied tinnitus, deafness, scotomas and hypotension when the latter were present.

The quinidin content of the plasma of twelve patients at the time of conversion of auricular fibrillation to sinus rhythm varied from 7.48 to 23.7 mg. per L. in six instances of rheumatic heart disease (including three conversions of the same patient at 10.8, 11.7 and 14) and 3.30 to 5.67 in six patients with coronary arteriosclerosis with or without hypertension. Two patients had not converted at the time quinidin therapy was stopped because of significant hypotension.

QUANTITATIVE STUDY OF QUINIDINE THERAPY. *Maurice Sokolow, M.D. and (by invitation) Archie L. Edgar, M.D., San Francisco, California.* (From the University of California Medical School.)

The quantitative aspects of quinidine therapy were investigated by determining multiple blood and urine quinidine levels in forty-one patients on varying dose schedules. The photofluorometric method of Brodie, as modified by Lilien-thal, was used. Sinus rhythm was re-established in thirteen of fifteen cases of auricular fibrillation or flutter. The amount of quinidine required for conversion, using the two or four-hour schedule, varied from 1.2 Gm. in twenty hours to 9.3 Gm. in ninety-six hours, with maximum blood levels of 2.0 to 13.7 mg./L. and an average of 7.0 mg./L. In only two cases was the level required for conversion less than 4 mg./L. In one case converted with a level of 7 mg./L. relapse occurred on maintenance doses with a level of 3.8 mg./L.; reconversion resulted when a level of 5.5 mg./L. was obtained with higher doses. In the two failures levels of 10 and 11 mg./L. were attained. In one case of ventricular tachycardia approximately 4 mg./L. was found to be the critical blood level preventing recurrent attacks. Four relapses occurred when the level was 3.3, 3.5, 3.3 and 2.5 mg./L. Sinus rhythm was reestablished at levels of 4.1, 4.3, 5.6 and 4.6 mg./L.

The average net peak level (subtracting the morning residual level resulting from the previous day's therapy) obtained with 0.2 Gm. every two hours for five doses was 3.9 mg./L.; for 0.4 Gm. every two hours for five doses, 4.9 mg./L.; for 0.6 Gm. every two hours for five doses, 5.5 mg./L.

When fixed daily doses were given every

four or six hours, a plateau was reached within seventy-two hours; it lasted three to four days and was followed by a gradual decline. The increment in blood level from single added doses was found to be 0.8 mg./L. with 0.2 Gm.; 1.2 mg./L. with 0.4 Gm. and 1.9 mg./L. with 0.6 Gm. The increment progressively decreased after the first two or three doses when the same dose was given every two hours. Comparable blood levels were reached in six observations when oral and intramuscular quinidine were given to the same patient.

An average of 49 per cent of the last evening level was still present in the blood approximately twelve hours later. Urinary excretion accounted for only 10 to 20 per cent of the total daily dose. Measurable blood levels were found as long as seventy-two hours and urine levels as long as forty-eight hours after quinidine was discontinued.

TAP WATER SODIUM IN A LOW SALT DIET. *Seymour L. Cole, M.D. (by invitation) and introduced by Edward Tyler, M.D., Los Angeles, California.*

Drinking water has frequently been overlooked as a source of sodium large enough to be considered when restricting that element in the solid part of the diet to 0.5 to 1.0 Gm. day.

Analyses of the tap water of the Los Angeles County General Hospital show it to contain 25 to 30 mg. sodium per 100 cc. The factors responsible are the high salt content of the original source, the Colorado River, and addition of salt in the Metropolitan Water District and in the hospital itself for softening purposes.

Study of the low salt diets of Schemm, Schroeder and others reveals them to allow 1,000 to 2,500 cc. and more of drinking water per day. In addition there are 500 to 600 cc. of hidden water used in the cooking of rice and preparation of leafy vegetables. Thus, an intake of 3,000 cc. of drinking water containing 30 mg. of sodium per 100 cc. in itself would provide 900 mg. of the allowed 1,000 mg. of sodium.

Therefore, to attain a low salt diet distilled water or low sodium content water should be substituted for tap water of high sodium content in addition to other precautionary measures.

OBSERVATIONS CONCERNING THE RISE AND FALL OF FREE AND ESTERIFIED CHOLESTEROL IN RATS MADE HYPERCHOLESTEREMIC BY A NEW METHOD. *Meyer*

Friedman, M.D. and (by invitation) S. O. Byers, Ph.D., San Francisco, California. (From the Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital.)

It was found possible to increase immediately the total cholesterol content of the rat's plasma approximately 600 per cent above the normal level by the intravenous injection of a new preparation of free cholesterol.

Immediately following such injections into 122 rats (30 mg. of cholesterol per 100 Gm. of body weight), the plasma free cholesterol content rose from a preinjection level of 12 to 295 mg. per 100 cc. However, no immediate rise occurred in the plasma esterified cholesterol. Three hours after the injection the free cholesterol fell to a value of 122 mg. per 100 cc. where it remained for approximately twelve hours. At this same time, however, the esterified cholesterol content of the rat's plasma rose to a value approximately twice that of the pre-injection level and it remained at this increased concentration for over twenty-four hours. At the end of thirty-six hours both the free and esterified cholesterol content of the rat's plasma had returned to pre-injection levels.

By means of this new technic the rate of disappearance as well as the partial esterification of injected free cholesterol was studied in a quantitative fashion.

EFFECT OF ENVIRONMENTAL TEMPERATURE ON THE FEBRILE REACTION TO TYPHOID PARATYPHOID VACCINES AND OTHER PYROGENS. *R. Grant, Ph.D. (by invitation), Marilyn Robbins, A.B., (by invitation) and V. E. Hall, M.D., Palo Alto, California.*

The febrile response to intravenous injection of pyrogens in rabbits includes inhibition of the mechanisms for heat dissipation (polypnea and cutaneous vasodilatation) and moderate increase of heat production. Oxygen production is maximal about twenty minutes after injection, and the increase is about 15 per cent of the control value for the first hour. This metabolic response is uniform at environmental temperatures from 31°C. to -5°C. and in completely shorn animals at -5°C. although control levels of oxygen consumption are about 110 per cent higher than normal under the last conditions. During the second and subsequent hours of fever

at moderate and high environmental temperatures oxygen consumption usually remains slightly increased, but in animals exposed to severe cold oxygen usage shows sharp reduction below control values during the second hour associated with shivering. Recovery to normal or supranormal values follows during the third hour. In consequence of this inhibition of cold defense profound hypothermia develops following initial slight fever. At normal temperatures the second hour is marked by reduced inhibition of heat defense mechanisms or partial defervescence, and the third hour by renewed febrile genesis. Similar effects are obtained with an endogenous pyrogen ("Pyrexin").

ACUTE CORONARY ARTERY OCCLUSION ASSOCIATED WITH EARLY ELECTROCARDIOGRAPHIC FINDINGS SUGGESTIVE OF PREDOMINANTLY SUBENDOCARDIAL INJURY. A "NEW" PATTERN OF MYOCARDIAL INFARCTION. *Hans H. Hecht, M.D. and (by invitation) Leonard W. Ritzmann, M.D. Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

It is assumed that predominantly subepicardial lesions of the heart muscle are characterized by electrocardiograms which display inversion of T and elevation of the RT segment in leads dominated by the effects of epicardial regions. In these leads subendocardial injury is suggested by upright T waves and by depression of the RT segment. As the exploring electrode of a unipolar system is primarily influenced by the electrical changes of adjacent tissues and to a much lesser degree by alterations in the electrical state of remote regions, subendocardial lesions must be more extensive than subepicardial involvement if changes of equal magnitude are to be recorded by an epicardial electrode. This is demonstrated in human subjects when pressure injury by a venous catheter exerted over a region of a few mm. may cause a monophasic deformation of the endocardial electrocardiogram but which leaves a simultaneously recorded electrocardiogram of the subjacent epicardial surface unaltered.

These considerations are supported by observations on four patients, all with angina pectoris of many years' duration, who entered the hospital with the typical signs and symp-

toms of recent myocardial infarction. The electrocardiograms taken within a few hours of the onset of the attack revealed striking displacement of the ST segment downward and in the opposite direction from the usual pattern. The QRS complexes were increased in voltage and lacked the characteristic Q waves. In one patient the typical pattern of anterior myocardial infarction emerged after ten hours, in another deep inversion of the terminal portion of the T waves without ST segment changes replaced the original pattern.

All patients died and postmortem examinations were performed on three. The examinations revealed recent myocardial infarction of the anterior wall of the left ventricle caused by complete closure of the descending branch of the left coronary artery in each instance. Extensive narrowing of the remaining coronary arteries was present in all, with widespread diffuse and patchy fibrosis of the left ventricular musculature in addition to the recent infarction. Subendocardial necrosis was outstanding in all.

It is concluded that the electrocardiograms demonstrated extensive subendocardial injury of the anterior wall. The endocardial injury was excessive because extensive narrowing of the vascular bed prior to the final occlusion prevented adequate collateral circulation.

The peculiar electrocardiographic pattern is a poor prognostic sign when seen during an episode of acute myocardial infarction.

EXPERIMENTAL INTERAURICULAR SEPTAL DEFECTS. *Sanford E. Leeds, M.D., William Birsner, M.D. (by invitation) and Orrin Cook, M.D. (by invitation), San Francisco, California.* (From The Harold Brunn Institute, Mount Zion Hospital.)

The production of interauricular septal defects by surgical means may become important if it could be shown that patients with severe mitral stenosis would be benefited by such a procedure. Closure of large congenital auricular septal defects would be most advantageous if an entirely satisfactory technic could be devised. For these reasons an operation which could be done with low mortality and no loss of blood, was developed for production of interauricular septal defects in dogs. After producing the defects the animals were studied with the catheter technic.

MECHANISM AND EFFICACY OF DIBENAMINE PROTECTION AGAINST SPONTANEOUS CYCLOPROPANE ARRHYTHMIAS IN SURGICAL PATIENTS. *Mark Nickerson, Ph.D. (by invitation) Hugh O. Brown, M.D., and Scott M. Smith, M.D. (by invitation), Salt Lake City, Utah.* (From the Departments of Pharmacology and Anesthesiology, University of Utah College of Medicine.)

The subjects of this study were healthy young adults undergoing elective surgery. Premedication was given with barbiturate, morphine and scopolamine. Patients were uniformly carried through all planes of surgical anesthesia to respiratory arrest and back to plane I over a period of about thirty minutes with unsupplemented cyclopropane. In plane IV and stage IV adequate oxygenation was maintained by pressure on the rebreathing bag, except for short periods during which the effects of anoxia were observed. Continuous electrocardiographic tracings, usually lead II, were obtained.

Control patients developed arrhythmias in all planes of surgical anesthesia. These irregularities increased exponentially with the depth of anesthesia. Ventricular tachycardia regularly developed in plane IV or stage IV. The arrhythmias were found to be accentuated by anoxia.

Premedication (one-half to twelve hours prior to operation) with 5 mg./Kg. of dibenamine only slightly reduced the incidence and severity of arrhythmias, but 7.5 mg./Kg. almost completely eliminated them. Such irregularities as did occur tended to increase exponentially with the depth of anesthesia as in the control series. No serious untoward reactions were noted.

Dibenamine protection against cardiac arrhythmias does not appear to be merely secondary to the effects of the drug on the peripheral circulation. The mean blood pressure in the three groups during anesthesia was not significantly different and the dose of dibenamine required to prevent cardiac arrhythmias was definitely higher than the dose (5 mg./Kg.) required to reverse the blood pressure response to epinephrine or sympathetic nerve activity in humans.

HYPERSENSITIVITY TO PENICILLIN. *J. F. Waldo, M.D. and Jeanne T. Tyson, B.A. (by invitation and introduced by M. M. Wintrobe) Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

In certain instances it has been possible to demonstrate by passive transfer, employing the Prausnitz-Küstner technic, a circulating antibody to penicillin. This passive transfer was possible only from those subjects with a severe reaction and then only during the most active phase of their reaction. The antigen employed for the passive transfer was crystalline penicillin dissolved in saline.

Experimental studies of penicillin sensitivity in animals are now in progress. By binding crystalline penicillin to pure human albumin we have been able to produce an antibody in rabbits which gives a fairly strong complement fixation reaction with the albumin-penicillin mixture after all reactivity to human albumin has been absorbed. Penicillin alone administered to the rabbit has failed to produce such an antibody. We also have some evidence that when penicillin is bound to human albumin the resulting antigenic product behaves in the manner of a mixed antigen while the human albumin used in the experiment behaves in the manner of a pure antigen. Quantitative studies of this antigen-antibody system are now in progress.

Inasmuch as it is known that penicillin does bind *in vivo* to albumin, it seems reasonable to suppose that when penicillin is administered to man the penicillin haptene coupled to albumin *in vivo* constitutes an antigen for the production of antibodies specific to this haptene group. This might well account for the penicillin sensitivity reactions that are observed in man.

EXCITATION OF HUMAN AURICULAR MUSCLE AND SIGNIFICANCE OF THE INTRINSICOID DEFLECTION OF THE AURICULAR ELECTROCARDIOGRAM. *Lowell A. Woodbury, Ph.D. (by invitation) and Hans H. Hecht, M.D., Salt Lake City, Utah.* (From the Departments of Physiology and Medicine, University of Utah College of Medicine.)

Electrocardiograms obtained by cardiac catheterization in man reveal a characteristic

form when the electrode is brought into contact with or closely adjacent to auricular muscle. The similarity of human records to those obtained from isolated muscle strips of lower animals is inescapable. It stimulated the re-examination of the "dipole" concept of the membrane theory of cardiac excitation and recovery.

Theoretical considerations support this concept. The wave of excitation may be viewed as a band in which the membrane is partially depolarized. The band is not sharply demarcated but shades from complete polarization on the leading edge to complete depolarization on the following edge. This is equivalent to two line charges of opposite sign the effective width of the band apart and submerged in a volume conductor. If a model is constructed or if the circles of equipotentials that arise from the two line charges are plotted and if a point representing the electrode is placed so that the moving line charges pass under or very close to the point, a diphasic curve may be constructed geometrically and expressed mathematically. The theoretical curve very closely resembles the recorded action potentials from human auricular muscle *in situ*.

Practical considerations deal with the definition and clinical application of the intrinsic deflection of Lewis which defines the moment that the band begins to pass under the electrode and the semidirect or intrinsicoid deflection of Wilson that defines a similar event for semidirect leads. It is demonstrated that with the exception of certain esophageal positions no true intrinsicoid deflection and no truly semidirect leads exist for auricular muscle in man. The impact of these considerations for the diagnosis of auricular enlargement and for the so-called pattern of mitral and pulmonic P waves will be discussed on the basis of observations obtained from detailed analysis of simultaneously recorded esophageal and precordial auricular leads.

Case Report

Chiari's Syndrome—Obliterative Endophlebitis of the Hepatic Veins*

HILARY H. HOLMES, M.D. and GEORGE MELCHER, M.D.

New York, New York

THE term Chiari's syndrome has been loosely applied in the past twenty years to many diseases in which there is obstruction or thrombosis of the hepatic veins, regardless of the underlying etiology. Chiari,¹ in 1899, described three cases which he believed fell into a separate pathologic entity, i.e., primary obliterative endophlebitis of the hepatic veins. He also included in his paper seven other cases in which the cause of death was an obliterative thrombosis of the hepatic veins but in which the thrombosis was thought to be secondary to another etiologic basis, e.g., peritonitis, congenital malformation of the hepatic veins, cirrhosis, etc.

Although Budd² first reported a case of hepatic vein occlusion, he recorded very few clinical details of the patient's course. The autopsy findings of peritoneal, pleural and pericardial adhesions which he described are compatible with the findings in polyserositis as the underlying cause of the occlusion.

Thirteen cases of hepatic vein thrombosis have been found in 15,300 consecutive autopsies performed by the Department of Pathology of Columbia University, but the one reported herein is the only one which falls under the heading of Chiari's syndrome as he described it. The lesions associated with hepatic vein obstruction in the other patients were carcinoma in four, sarcoma in two, liver abscesses in three, operative procedure in one (porta-caval shunt), cavernomatous transformation of

the portal vein in one and polycythemia vera in one. Any lesion which may involve the hepatic veins due to proximity or which causes generalized thrombosis, such as neoplasms, scars, inferior vena caval thrombosis, abscesses, gummas, enlarged lymph nodes, polycythemia vera and many others, may produce occlusion of the hepatic veins. Recently all of these diseases have been lumped together under the term Chiari's syndrome (Budd's syndrome might be more appropriate as Chiari distinguished between this secondary type of obstruction and that due to primary thrombosis).

The basis for primary obliteration of the hepatic veins has not been adequately explained. Chiari believed that the underlying process was an inflammation of the vein wall whereas Thompson and Turnbull³ suggested thrombophlebitis as its cause, the changes in the vein walls being secondary to the thrombi. Satke⁴ reported four cases of obliterative endophlebitis of the hepatic veins, and he presented histologic evidence for Chiari's contention that the primary change is thickening of the endothelium of the vein wall and that thromboses are secondary. Kelsey and Comfort⁵ summarized the theories for the predilection for the hepatic veins as a site for thrombosis. They pointed out that retardation of flow at the diaphragmatic level by pressure changes in the thorax along with mechanical factors at the ostia of the veins which suspend the liver from the vena cava might be factors in the pathogenesis of thrombosis. Other hypotheses include Rosenblatt's⁶ idea of

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congenital occlusion of the hepatic veins, and Moore's⁷ theory of reactivation of the tendency to obliteration such as occurs in fetal ductus venosus. Hutchinson and Simpson⁸ suggested that the intra-uterine obliteration of the venae revehentes might continue too far. Whatever the pathogenesis, hepatic vein occlusion is extremely rare and invariably fatal.

Hirsh and Manchester⁹ summarized the seventy cases reported up to 1946 and discussed the various causes of obstruction of the hepatic veins. They pointed out that there is an acute and a chronic form of the disease, depending upon whether the occlusion is partial or complete and whether recanalization occurs. Although the disease may occur at any age, over 50 per cent of the reported cases occurred between the ages of twenty and forty. Both sexes are equally affected.

The clinical symptoms reflect the rapidity of the process of occlusion. Invariably the first symptom is abdominal pain or discomfort, most marked in the upper abdomen. This may continue for months before the patient seeks medical assistance, or it may be sudden and severe. Abdominal enlargement is usually noted by the patient or his friends. A history of icterus is unusual. In cases of several months' duration peripheral edema is usually present.

The acute form and the terminal episode in the chronic form of the disease is that of severe upper abdominal pain resembling an abdominal catastrophe, vomiting and rapid enlargement of the abdomen. Upon examination the patient is usually in shock. There is splinting of the abdomen, marked enlargement and tenderness of the liver, ascites and splenomegaly, again depending upon the rapidity of occlusion. Mild icterus and acidosis may now be present. Coma rapidly ensues and death due to hepatic insufficiency occurs within a few hours to a few days.

Experimentally, the syndrome has been reproduced in animals. Simonds and Callaway¹⁰ produced sudden complete obstruction of the hepatic veins in dogs, causing

marked enlargement of the liver, shock and rapid death similar to the pattern in Chiari's syndrome.

The case to be described very closely resembles the first of the three cases which Chiari described, and the autopsy findings are typical of the other cases reported in the literature.

CASE REPORT

A. F., a twenty-three year old white female proof-reader, was transferred in coma to the Presbyterian Hospital from the Muhlenberg Hospital in Plainfield, N. J., on April 22, 1947.

Her past history, taken from the patient at that hospital, revealed vague abdominal pain, gradual enlargement of her abdomen and a weight gain of 23 pounds over the past year. Her diet had been deficient in protein and her alcoholic intake had been excessive for more than two years. Six months before admission she had fallen from a horse and sustained a head injury with a large facial hematoma but had not lost consciousness or had any other signs of central nervous involvement. In 1942 she had an attack of primary atypical pneumonia from which she recovered completely. During the past few months she had had several attacks of upper abdominal distress, the last episode being one month before when she had experienced rather severe epigastric pain, anorexia, nausea and vomiting. This attack lasted only twenty-four hours. At no time had she been noted to have any signs, symptoms or hematologic findings of polycythemia vera. She had not been exposed to hepatotoxins or jaundiced persons. Six days before admission she had been vaccinated with smallpox vaccine.

The onset of her present illness was forty-eight hours before admission to the Muhlenberg Hospital when during the morning she began to have intermittent upper abdominal "gas" pains. Shortly after the onset the pains became generalized throughout her abdomen and were moderately acute. The following day she experienced some nausea and vomiting and took several enemas, productive of brown stools, with temporary relief. About one hour after her evening meal on the second day of her illness the pains and vomiting recurred with increased severity.

A physician was called at that time and he noted that her liver was enlarged. He administered a sedative and advised hospitalization.

However, she remained at home and was seen again the following morning. At this time she was in profound shock and was immediately hospitalized.

Upon admission to the Muhlenberg Hospital her temperature was 94.4°F., apical pulse 88, respirations 32 (regular). The blood pressure was unobtainable. She was somnolent and slightly cyanotic although she was sufficiently alert to give a satisfactory history. She complained of drowsiness, shortness of breath and pain in her right shoulder since early morning. Her pupils were constricted and reacted sluggishly to light. The fundi showed engorged veins. The only other positive physical findings were a distended abdomen containing a fluid wave, liver enlarged to 8 cm. below the costal border and spleen enlarged to 5 cm. below the costal border. No peripheral pulses were palpable.

Admission studies revealed the following: hemoglobin 21 Gm. (145 per cent); red blood cells 11,680,000; white blood cells 44,900 (neutrophils 89, lymphocytes 11, eosinophiles 1); hematocrit 85 per cent (checked on two specimens of blood); non-protein nitrogen 67 mg. per cent; serum uric acid 5 mg. per cent; cholesterol 210 mg. per cent; icterus index 8; serum chlorides 400 mg. per cent; CO₂ 28 volumes per cent; serum proteins 11.4 Gm. per cent (by the copper sulfate method and checked by the Kjeldahl method); urine albumin 4 plus, with occasional red blood cell and white blood cells in the microscopic examination.

A 500 cc. phlebotomy was performed and 1,500 cc. of saline administered. Shortly after the phlebotomy and the infusion of saline a repeat count showed that the red blood cells had fallen to 8,320,000, hemoglobin to 20.7 Gm. and hematocrit to 77 per cent. Leukocytosis increased to 62,400 with 89 per cent neutrophils. The blood smear was reported to show 2 per cent myelocytes, many large platelets but no myeloblasts.

During the day her blood pressure ranged from 80/60 to 118/80. Her temperature rose to 100.2°F. during the evening of the first day in that hospital. She was very restless all day but no sedatives were administered. Heparin, 10 mg., was given intravenously soon after admission, and another 15 mg. within three hours, but no venous clotting times were recorded.

Twelve hours after admission, following intravenous administration of 3,000 cc. of 5 per cent glucose in water, the total protein had

fallen to 5.75 Gm. A blood count then showed further reduction of red blood cells to 7,800,000 and a hemoglobin of 17.5 Gm. (120 per cent). At that time she was rational, with less discomfort and was sitting up talking to her family. Later that evening she lapsed into a coma and on the following morning, April 22, 1947, she was transferred to the Presbyterian Hospital. Immediately prior to transfer the red count was 6,350,000, white blood cells 28,600 (89 per cent neutrophils) and hematocrit 55 per cent. Other laboratory reports from that hospital showed a slightly positive reaction for blood in her feces and vomitus.

Physical examination upon admission to Presbyterian Hospital revealed a dark-complexioned, young adult female in a deep coma. Her temperature was 98.2°F., pulse 100, respirations 28, and blood pressure in the left arm 112/80. She responded only to painful stimuli. Her skin was cool and moist, with no eruption, petechiae, cyanosis or jaundice but had a peculiar alabaster hue. Her entire body seemed edematous but no pitting could be made out. She was breathing deeply, and an "amine odor" was noted on her breath. The pupils were widely dilated, equal and reacted sluggishly to light. Her conjunctivae were injected and the right cornea had a small abrasion over its surface. Her sclerae were not icteric and the fundi were normal. The jaw was held rigidly in trismus; her tongue was abraded from bites and she was intermittently grinding her teeth together. Ear, nose and throat examination was otherwise normal. The neck was supple and glandular adenopathy was not present. The lungs were clear. The heart was not enlarged; there was regular sinus rhythm; sounds were of good quality. No murmurs were heard and A₂ equalled P₂. The abdomen was distended and a fluid wave was present. The liver was enlarged to 5 finger-breadths below the costal margin, was firm, not nodular and pressure over it caused groans from the patient. The spleen could not be palpated and no other masses or organs were noted. Rectal examination was negative and the stool specimen obtained was brown and guaiac negative. The extremities exhibited intermittent episodes of spasm or tonic contractions. Reflexes were equal and active throughout and inconstant Babinski signs were present. The abdominals and ankle jerks were absent. The Chvostek sign was positive but the Trousseau was negative.

Laboratory findings on admission were: hemoglobin 17.5 Gm.; red blood cells 5,500,000; white blood cells 43,500 with 92 per cent neutrophils; platelets 668,000; erythrocyte sedimentation rate 0; hematocrit 60.9 per cent; urine specific gravity 1.008, acid reaction, albumin 3 plus, glucose negative, bile negative and upon microscopic examination 10 to 12 red blood cells per high power field as well as 40 to 50 white blood cells per high power field were seen. Serum urea nitrogen 36 mg. per cent; serum sugar (with 5 per cent dextrose infusion running into the opposite arm) 133 mg. per cent; alkaline phosphatase 9.5 Bodansky units; serum bilirubin 2.3 mg. per cent; cholesterol 61 mg. per cent; cephalin flocculation 4 plus; serum protein 4.6 Gm. per cent (albumin 4.0 and globulin 0.6); Kline test negative; serum amylase 44 Myers and Killian units; prothrombin time 35 seconds (normal 14 ± 1 seconds); CO_2 41.5 volumes per cent; serum chlorides 86.7 mEq./L.; serum calcium 8.3 mg. per cent; venous clotting time three minutes and forty-five seconds; blood culture showed no growth; x-ray of the chest revealed no evidence of pulmonary disease; x-ray of the abdomen showed ascites, with a single gas-filled loop of small intestine on the right side. The patient was seen by a surgical consultant who thought that there were no indications for abdominal exploration. A neurologic consultant agreed that her central nervous system symptoms were undoubtedly due to hepatic insufficiency but added that postvaccinal encephalitis might also be complicating the picture. A lumbar puncture was done, with normal pressure findings and no cells were found in the spinal fluid.

She remained in a deep coma and was treated with 600 cc. of plasma and almost continuous intravenous glucose which was administered slowly. Eight hours after admission the hematocrit had fallen to 54 per cent. She was also given penicillin in a dosage schedule of 100,000 units every three hours. She was catheterized every six hours, but only 110 cc. of urine were obtained over the twenty-three hour period. Twenty hours after admission it was noted that she was definitely icteric, that the liver was larger by 2 finger-breadths, the spleen was palpable and more ascites had accumulated. Her urine showed 1 plus bile. Blood studies then showed a hematocrit of 49 per cent; alkaline phosphatase of 10.2 Bodansky units; bilirubin 3.4 mg. per cent; serum urea nitrogen

53 mg. per cent and serum amino acid nitrogen of 5.5 mg. per cent.

Her course was progressively downhill and her temperature rose to 102.8°F . Twenty-three hours after admission she suddenly became cyanotic and ceased breathing.

The significant findings at autopsy were the following: Grossly, the abdomen was moderately distended. When the incisions were made, the subcutaneous tissues of the trunk and body musculature appeared to be water-logged. Two hundred cc. of clear yellow fluid were found in each thoracic cavity, 2 liters of fluid of a similar nature were present in the peritoneal cavity. Large masses of coagulated protein material were pulled away from the retroperitoneal spaces. The heart weighed 260 Gm. and was not remarkable, except for three small, stringy clots in the right auricle and ventricle.

The lung surfaces were wet and mottled, purple-red and yellow. There was moderate congestion and edema on section, and the base of the right lower lobe was atelectatic.

The spleen was markedly enlarged, weighed 620 Gm. and was more firm than usual. Throughout its substance could be seen a few whitish nodules averaging 2 mm. across. One larger nodule raised the capsule slightly. All appeared spherical on section.

The liver was markedly enlarged and weighed 2,500 Gm. The whole organ had the usual consistency. Its color was derived from two elements: confluent, irregularly rounded, yellow spots averaging 2 mm. across and standing out against the dark purple background. Upon section the details were clearer, with yellow portions projecting above the dark, bloody background, suggesting swollen lobules surrounded by hemorrhagic and necrotic stroma. Throughout the parenchyma, white, firm, fibrous, cord-like structures were encountered on multiple section, the manner of their branching suggesting blood vessels. Occasionally the structure of a vein could be discerned, occluded with connective tissue and sometimes partially canalized. Another lesion seen on multiple section was an irregular, opaque, soft mass of tissue of a paler yellow, through the center of which there was a vein occluded by a thrombus. A similar soft thrombus was found adherent to the wall of one of the main intrahepatic branches of the portal vein, with other thrombi found in the lumen of the portal vein as it was followed into the mesentery. (Figs. 1 and 2.)



FIG. 1. Gross appearance of liver. Thrombi are present in nearly all of the larger hepatic vein radicles. In the center of the infarct on the right is a vein occluded by a thrombus.

FIG. 2. Another section of liver showing extreme congestion, patchy infarction and thrombosis.

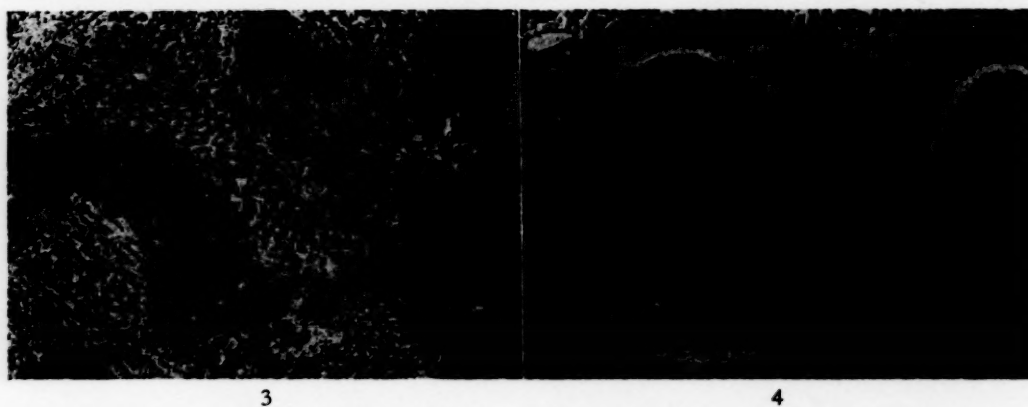


FIG. 3. Low power microscopic section of the liver. The sparing of the periportal areas by the hemorrhagic coagulative necrosis is well illustrated.

FIG. 4. This low power section shows two hepatic vein radicles partially occluded by recent thrombi, some inflammatory reaction within the vein walls and necrotic liver parenchyma adjacent to the veins.

The kidney cortices were unusually homogeneous, smooth, red-brown in color and without distinguishing landmarks. The capsules stripped easily, and the pelves and calyces were not remarkable. The right ovary contained a 2 cm. cyst. The intestinal wall was thickened with edema and its mucosa was congested.

The thyroid and the bone marrow were not unusual, except that they were redder than is ordinarily found.

The gyri of the cerebrum were slightly flattened and the sulci correspondingly narrowed throughout. Otherwise, there were no remarkable gross findings.

The significant microscopic findings were the following: The heart showed an area of diffuse hemorrhage in the myocardium close to the epicardium of the left ventricle. A small, free thrombus was noted adjacent to the endocardial surface of the right ventricle and its sectional outline was rounded, suggesting an origin within a small vessel.

In the lungs there was a slight amount of coagulated protein material in certain alveoli.

Many alveoli were filled with red blood cells. Small thrombi were found in many of the smaller pulmonary artery radicles, one showing almost complete organization.

The spleen showed chronic congestion, and section through the largest aspect of the subcapsular whitish nodule showed it to be circumscribed. It compressed the adjacent parenchyma, indicating expansile growth. The small tumor was composed of tissue resembling red pulp, with exaggerated sinusoidal walls, containing no Malpighian corpuscles. It was considered to be a benign hamartoma.

In the liver there was widespread congestion and hemorrhagic coagulative necrosis which, as a rule, spared the periportal areas. Thrombi were found in the hepatic veins, frequently attached to their walls. (Figs. 3 and 4.) There was marked inflammatory reaction in the walls of some small veins. A large vein, half-occluded, showed strands of pink-staining fibrin-like material in its wall. The wall was thin at several points and at one point was broken and a patch of new fibrous tissue was present. Outside some



FIG. 5. A high power view of a thrombosed vein in which complete organization and recanalization have occurred.

FIG. 6. In this section there is a vein partially occluded by an old, organized thrombus with superimposed fresh thrombosis.

of the veins the connective tissue was quite edematous. Some veins were completely organized and showed varying degrees of canalization. (Figs. 5 and 6.)

The kidneys had congested glomeruli. The convoluted tubules contained a granular precipitate and appeared slightly distended. The proximal convoluted tubular cells projected into the lumina. The cytoplasm of all the cells was homogeneous and granular. In the collecting tubules masses of granular, red-staining material were seen. One of the pelvic veins showed an edematous wall and contained several rounded pieces of thrombus.

The bladder was not remarkable except for occlusion of a small artery by fibrous tissue. A vein in one of the Fallopian tubes was blocked and distended by a thrombus as were one artery and several veins in the ovaries and mesovarium. There were veins in the mesentery containing thrombi either completely or partially occluding them.

The stomach, small intestine and colon showed edema of the muscular layers and occasional veins containing fragments of thrombi.

The bone marrow showed an increase in the megakaryocytes in all fields.

The only lesion of note in the brain and spinal cord, other than a congenital extradural cyst with herniation of the arachnoid membrane at the eighth thoracic vertebral level, was congestion and edema of the brain.

Anatomic diagnoses were as follows: thrombi in the hepatic veins; thrombi in many small veins, generalized; necrosis of the liver; ascites and hydrothorax, bilateral; edema of the brain; emboli in the smaller pulmonary arteries;

increase in the bone marrow megakaryocytes; benign hamartomas of the spleen.

COMMENTS

The case herein reported, of obscure etiology, is believed to be fairly typical of the independent obliterative endophlebitis of the hepatic veins seen in the three cases described by Chiari,¹ and in several of the cases reported by Hess¹¹ and Satke.⁴

The sudden terminal episode of severe abdominal pain, shock of an extreme nature, and coma and death due to hepatic insufficiency was due undoubtedly to the final, almost complete occlusion of the hepatic veins resulting in massive congestion and necrosis of the liver parenchyma.

The intermittent bouts of upper abdominal pain and abdominal swelling in the months prior to the final episode were probably associated with the inflammatory process in the hepatic veins and occlusion of smaller radicals. The history of trauma six months before death must be considered to have a possible rôle in the etiology, but there were no immediate abdominal symptoms nor were there any in the two months following her accident. Thrombosis of the hepatic veins is one of the most serious complications of polycythemia vera,¹² and in this case that diagnosis was suggested in the beginning because of the extreme hemoconcentration. It was believed that this dyscrasia was ruled out by the fact that

she had never had any suspicion of polycythemia previously, that her plasma proteins were 11.4 Gm. per cent when she was polycythemic and on subsequent hydration fell even to below normal limits, that she was in profound shock at the time her high red count and hematocrit were taken and that her bone marrow was not hyperplastic on microscopic examination.

Thromboses occurred in many other vessels throughout the body in addition to those in the hepatic veins, and somewhat similar findings have been seen in the syndrome of acute febrile anemia and thrombocytopenic purpura with capillary platelet thromboses described by Moschkowitz¹³ and Baehr.¹⁴ However, the elevated platelet count in this case and the absence of purpura, anemia and generalized capillary and precapillary hyaline thrombi differentiates this case from those. The complete intrahepatic thromboses and massive necrosis of the liver make the thromboses elsewhere in the body assume only secondary importance although they are undoubtedly based upon the same etiology whatever that may be.

Sproul¹⁵ reviewed the occurrences of multiple venous thromboses in carcinoma of various sites, especially in the body and tail of the pancreas, but in the absence of carcinoma this warrants only passing consideration in the differential diagnosis of this unusual lesion.

SUMMARY

A case of Chiari's syndrome, idiopathic obliterative endophlebitis of the hepatic veins, is presented with the clinical and pathologic findings.

A distinction is made between obliterative endophlebitis of the hepatic veins as seen in this syndrome and occlusion due to other

intrahepatic or extrahepatic diseases in which the hepatic veins are secondarily involved.

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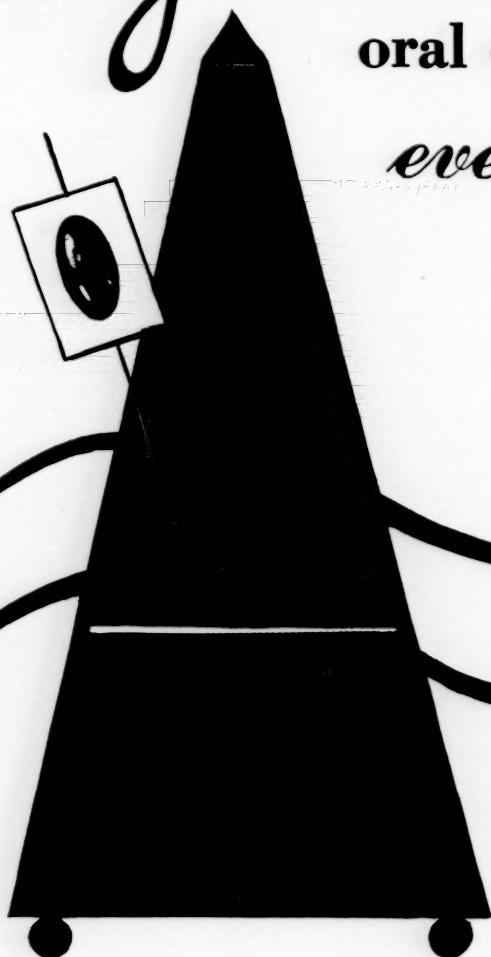


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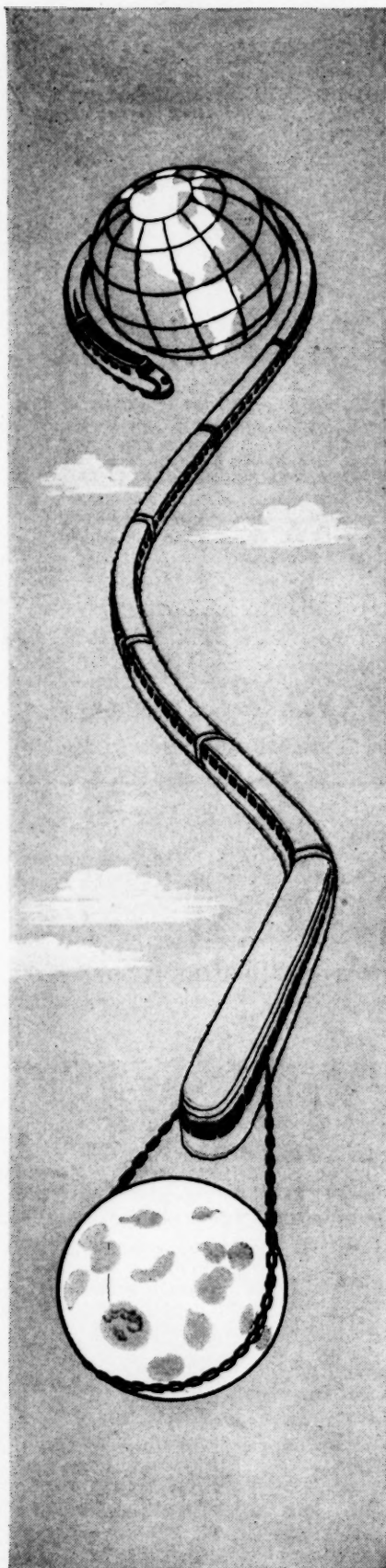
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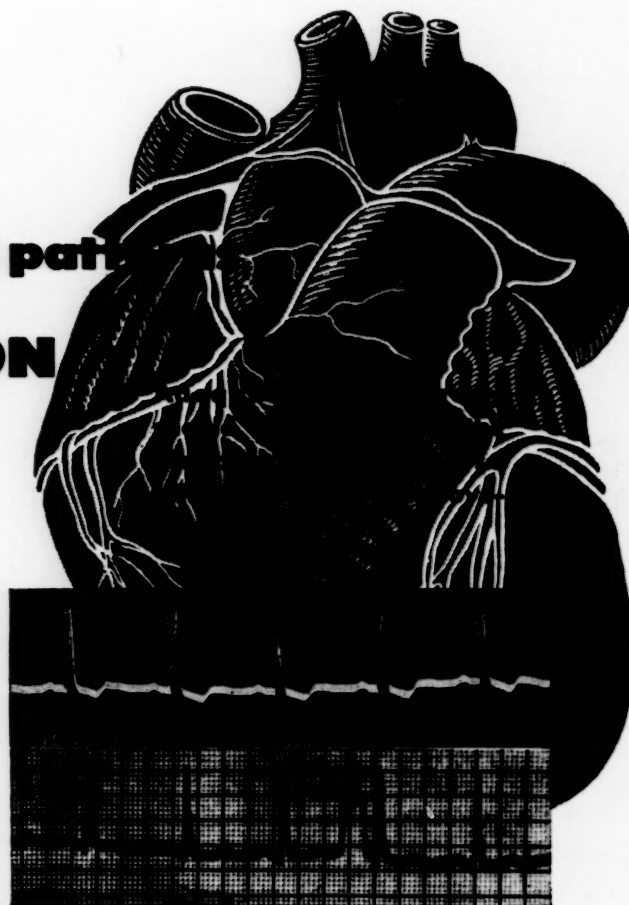
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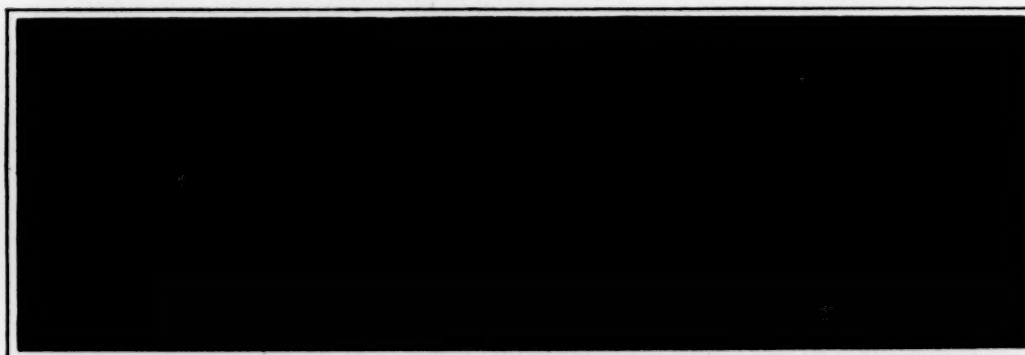
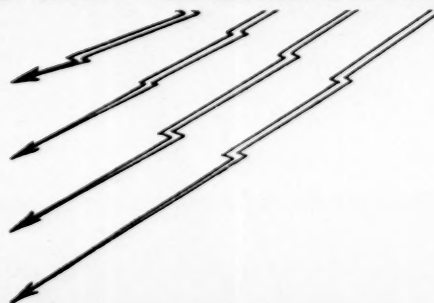
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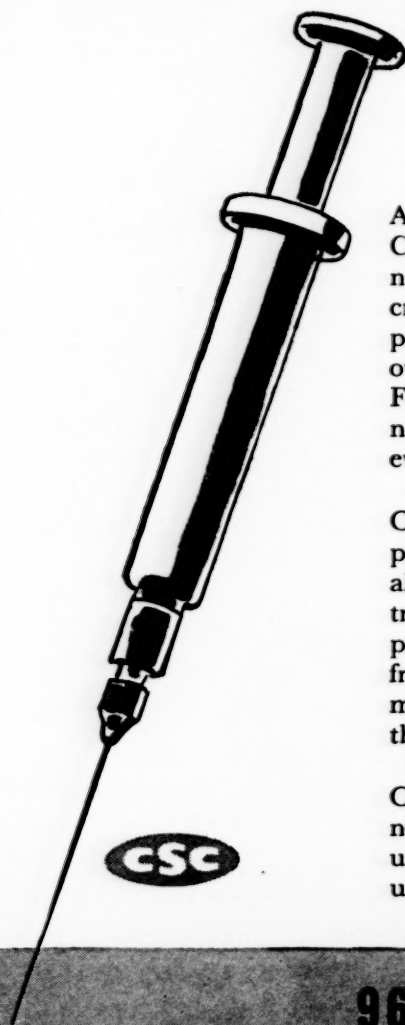
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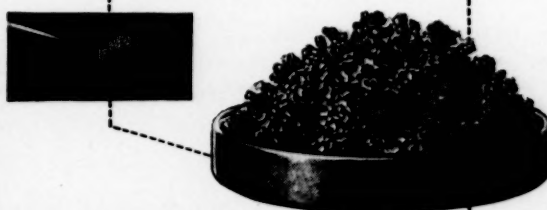
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Administration prior to or concurrently with digitalization avoids driving the faltering heart against an accumulated fluid burden and prevents the overdigitalization which may occur when postponed diuretic therapy mobilizes previously administered cardioactive glycosides from edema fluid.⁹

DOSAGE: 1 cc. or 2 cc. intramuscularly or intravenously, given daily, or as indicated, until a weight plateau is attained. Subsequently the interval between injections is prolonged to determine the maximum period permitted to intervene between maintenance injections.

PACKAGING: MERCUHYDRIN (meralluride sodium) is available in 1 cc. and 2 cc. ampuls.

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